2.HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of vinyl chloride. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowestobserved-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify

these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals or exposure levels below which no adverse effects have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of vinyl chloride are indicated in Tables 2-l and 2-2 and Figures 2-l and 2-2. Because cancer effects could occur at lower exposure levels, the figures also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in l0,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for vinyl chloride. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancer health effects only and do not reflect a consideration of carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1989a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in

development or result from repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

A report by Danziger (1960) described the deaths of two vinyl chloride workers. In one case, a worker exposed to high concentrations of vinyl chloride vapor emitted from an open valve was found dead. In another case, a worker responsible for cleaning a polymerization tank was found dead in the tank. Autopsies performed on these men showed congestion of the internal organs, particularly the lungs and kidneys, and failure of the blood to clot. Circumstances surrounding the deaths suggested that the deaths were due to breathing very high levels of vinyl chloride. No increase in mortality was noted in a prospective cohort study of 1,100 workers exposed to vinyl chloride compared to the controls (Laplanche et al. 1992). At the time of the study interview, 36% of the 1,100 workers were currently being exposed to vinyl chloride, and 64% had been exposed in the past (Laplanche et al. 1987, 1992).

Brief exposures to concentrations of vinyl chloride ranging from 100,000 to 400,000 ppm have been shown to be fatal in experimental animals such as rats (Lester et al. 1963; Mastromatteo et al. 1960), guinea pigs (Mastromatteo et al. 1960; Patty et al. 1930), and mice (Mastromatteo et al. 1960). At these concentrations, deaths occurred within 30-60 minutes. Male mice exposed to 30,000 ppm vinyl chloride for 5 days, 6 hours per day, in a dominant lethal study showed increased mortality (Anderson et al. 1976). Increased mortality was also observed at much lower concentrations in maternal mice in a developmental toxicity study (John et al. 1977, 1981). In this study, maternal mice had an increased incidence of deaths following exposure to 500 ppm for 10 days during gestation.

Decreased longevity was observed in intermediate-duration studies (Adkins et al. 1986; Drew et al. 1983; Feron et al. 1979a; Hong et al. 1981; Lee et al. 1978) and chronic-duration studies (Drew et al.

1983; Feron et al. 1979a; Viola 1970). A treatment-related increase in mortality was observed in mice exposed to 500 ppm of vinyl chloride for 6 hours per day, 5 days per week, for 6 months (Adkins et al. 1986). In mice and rats maintained for 12 months following a 6-month, 6-hour-per-day, 5-day-perweek exposure regime, decreased longevity was observed at concentrations as low as 50 ppm (Hong et al. 1981). However, statistical analyses of the data were not available to verify the significance of the decrease. Substantial increases in mortality of mice and rats exposed to 250 ppm vinyl chloride for 12 months were observed by Lee et al. (1977a, 1978). In addition, small increases in mortality of mice and rats during the 1Zmonth exposure period were observed at 50 ppm in these reports. However, statistical analyses indicating the significance of these increases were not presented.

The influence of the age of female animals at the time of exposure to vinyl chloride on survival was examined by Drew et al. (1983). In female hamsters exposed to 200 ppm, two strains of female mice exposed to 50 ppm, and female rats exposed to 100 ppm for 12 months, a higher death rate was observed when 2-month-old animals were exposed than when 8- or 14-month-old animals were exposed. Similar trends were observed when hamsters and mice were exposed to these concentrations for 6 months. Thus, it appears that younger animals may be more susceptible to the lethal effects of vinyl chloride. These results do not necessarily indicate that young people are more susceptible to the lethal effects of vinyl chloride, since animals that were exposed later in life may have died of age related causes prior to the expression of the lethal effects. This study was limited in that only one dose of vinyl chloride was tested in each species.

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each study with a systemic end point in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects. Limited information is available on the acute effects from inhalation of vinyl chloride by humans. Autopsy findings from a man who died after being overcome by vinyl chloride vapor revealed the irritating nature of extremely high-level inhalation exposure. The lungs were found

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (NS)	30 min				300000 (5/5 died)	Mastromatteo et al. 1960
2	Mouse (CD-1)	5 d 6hr/d				30000 M (11/20 died)	Anderson et al. 1976
3	Mouse (CF-1)	10 d 7hr/d Gd6-15				500 F (17% maternal death)	John et al. 1977, 1981
4	Mouse (NS)	30 min				200000 (1/5 died)	Mastromatteo et al. 1960
5	Gn pig (NS)	30 min				300000 (1/5 died)	Mastromatteo et al. 1960
6	Gn pig (NS)	up to 8 hr				100000 (death)	Patty et al. 1930
	Systemic						
7	Rat (Holtzman)	1, 5 d 6hr/d	Hepatic	50000 M	100000 M (hepatocellular vacuolization, increased AKT and SDH)		Jaeger et al. 1974

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)	Reference
8	Rat (NS)	30 min	Resp			100000	(lung hyperemia)		Mastromatteo et al. 1960
			Hepatic	100000		200000	(fatty infiltration changes)		
			Renal	200000		300000	(renal congestion)		
9	Rat (Holtzman)	1, 5 d 6hr/d	Hepatic	50000					Reynolds et al. 1975a
10	Rat (NS)	1 d 6hr/d	Hepatic	50000	M				Reynolds et al. 1975b
11	Mouse (NS)	30 min	Resp			100000	(lung hyperemia)		Mastromatteo et al. 1960
			Hepatic	200000		300000	(liver congestion)		
			Renal			100000	(degenerative tubular epithelium)		
12	Gn pig (NS)	30 min	Resp			100000	(slight pulmonary hyperemia)		Mastromatteo et al. 1960
			Cardio	400000					
			Hepatic	200000		300000	(fatty degeneration)		
			Endocr	400000					
			Ocular	400000					

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)		Reference
	Immuno/Lymphor								
13	Gn pig (NS)	30 min		400000					Mastromatteo et al. 1960
	Neurological								
14	Human	3 d 2x/d 5min		4000	8000	NS (dizziness)			Lester et al. 1963
15	Rat (Fischer- 344)	1 hr		50000					Hehir et al. 1981
16	Rat (Fischer- 344)	2 wk 5d/wk 1hr/d		500					Hehir et al. 1981
17	Rat (Holtzman)	1, 5 d 6hr/d		50000 M			100000 M	(anesthesia)	Jaeger et al. 1974
18	Rat (Sherman)	2 hr			50000	(moderate intoxication)			Lester et al. 1963
19	Rat (NS)	30 min					100000	(narcosis)	Mastromatteo et al. 1960

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)		Reference
20	Mouse (ICR)	1 hr		5000				50000	(ataxia)	Hehir et al. 1981
21	Mouse (NS)	30 min						100000	(narcosis)	Mastromatteo et al. 1960
22	Gn pig (NS)	30 min						100000	(tremor, loss of consciousness)	Mastromatteo et al. 1960
23	Gn pig (NS)	up to 8 hr		10000				25000	(narcosis)	Patty et al. 1930
	Reproductive									
24	Mouse (CD-1)	5 d 6hr/d		30000	M					Anderson et al. 1976
	Developmental									
25	Rat (Sprague-Dawley)	10 d 7hr/d Gd6-15				2500	(ureter dilation)			John et al. 1977, 1981
26	Mouse (CF-1)	10 d 7hr/d Gd6-15		50 [b]		500	(delayed ossification)			John et al. 1977, 1981

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)			LOAEL (effect) Serious (ppm)		Reference
27	Rabbit (New Zealand)	13 d 7hr/d Gd6-18				500		(delayed ossification)			John et al. 1977, 1981
	Cancer										
28	Mouse (ICR)	1 hr							5000	(CEL: bronchioalveolar adenoma)	Hehir et al. 1981
	INTERMEDIATE EXPOSURE										
	Death										
29	Rat (CD)	1-10 mo 5d/wk 6hr/d							50	(17/26 died)	Hong et al. 1981
30	Mouse (A/J)	6 mo 5d/wk 6hr/d							500 M 500 F	(37/70 died) (23/70 died)	Adkins et al. 1986
31	Mouse (CD-1)	1-6 mo 5d/wk 6hr/d							50	(15/16 died)	Hong et al. 1981
	Systemic										
32	Rat (Wistar)	3 mo 6d/wk 6hr/d	Cardio	10	M	100	M	(increased relative heart weight)			Bi et al. 1985
			Renal	100	M	3000	M	(increased relative kidney weight)			

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)	Reference
33	Rat (Wistar)	6 mo 6d/wk 6hr/d	Cardio			10	M	(increased relative heart weight)	Bi et al. 1985
			Hepatic			10 [c]	M	(increased relative liver weight)	
34	Rat (Sherman)	19 d 8hr/d	Hemato			50000		(decreased white blood cells)	Lester et al. 1963
			Hepatic			50000		(hepatocellular hypertrophy, large irregular vacuoles, compression of sinusoids, elevated relative liver weight)	
			Renal	50000					
			Derm	50000	F	50000	M	(thin coats, scaly tails)	
35	Rat (Sherman)	92 d 5d/wk 8hr/d	Hemato			20000		(decreased white blood cells)	Lester et al. 1963
			Hepatic			20000		(moderate hepatocellular hypertrophy, fine to medium vacuoles, compression of sinusoids)	
			Renal	20000					

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)			LOAEL (effect) Serious (ppm)	Reference
36	Rat (Wistar)	10 mo 5d/wk 5hr/d	Musc/skel	20000	M					Sokal et al. 1980
			Hepatic			50	M	(fatty changes)		
			Renal	50	M	500	M	(increased kidney weight)		
			Bd Wt			50	M	(10% decrease in body weight)		
37	Rat (NS)	6 mo 5d/wk 0.5-7hr/d	Hemato	200						Torkelson et al. 1961
			Hepatic			100		(increased relative liver weight)		
			Renal	200						
			Bd Wt	200						
38	Rat (Wistar)	10 mo 5d/wk 5hr/d	Hepatic			50	M	(fatty changes)		Wisniewska-Knypl et al. 1980
39	Mouse (NS)	1-6 mo 5d/wk 5hr/d	Hepatic			2500	M	(hyperplasia of hepatocytes and activated sinusoidal cells)		Schaffner 1978
40	Mouse (CD-1)	8 wk 5d/wk 6hr/d	Hemato	1000	M					Sharma and Gehring 1979
			Hepatic			1000	M	(decreased liver weight)		
			Renal	1000	M					
			Bd Wt	1000	M					

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)			LOAEL (effect) Serious (ppm)		Reference
41	Mouse (CD-1)	5-6 mo 5d/wk 5hr/d	Resp			2500	M	(proliferation and hypertrophy of bronchial epithelium; hypersecretion of mucin; hyperplasia of alveolar epithelium)			Suzuki 1978, 1981
42	Rabbit (NS)	6 mo 5d/wk 7hr/d	Hepatic	100					200	(centrilobular degeneration and necrosis)	Torkelson et al. 1961
			Renal	200							
			Bd Wt	200							
	Immuno/Lymphor										
43	Rat (Wistar)	3 mo 6d/wk 6hr/d		100	M	3000	M	(increased spleen weight)			Bi et al. 1985
44	Rat (Wistar)	6 mo 6d/wk 6hr/d				10	M	(increased spleen weight)			Bi et al. 1985
45	Rat (Wistar)	10 mo 5d/wk 5hr/d				50	M	(increased spleen weight)			Sokal et al. 1980
46	Mouse (CD-1)	2-8 wk 5d/wk 6hr/d				10	M	(increased spontaneous lymphocyte proliferation)			Sharma and Gehring 1979

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)			LOAEL (effect) Serious (ppm)			Reference
	Neurological											
47	Rat (Fischer- 344)	20 wk 5d/wk 1hr/d		50								Hehir et al. 1981
	Reproductive											
48	Rat (Wistar)	3, 6 mo 6d/wk 6hr/d		10	M	100	M	(decreased testes weight)				Bi et al. 1985
49	Rat (CD)	11 wk 5d/wk 6hr/d		50	M				250	M	(reduced male fertility)	Short et al. 1977
50	Rat (Wistar)	10 mo 5d/wk 5hr/d		50	M				500	M	(spermatogenic epithelial necrosis)	Sokal et al. 1980
	Cancer											
51	Rat (Fischer- 344)	6 mo 5d/wk 6hr/d							100	F	(CEL: hepatic hemangiosarcoma, hepatocellular carcinoma, neoplastic nodules; mammary fibroadenoma)	Drew et al. 1983

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
52	Rat (Sprague-Dawley)	33 d 6 d/wk 8 hr/d				500 M (CEL: hepatocellular carcinoma, angiosarcoma of the liver, benign cholangioma, nephroblastoma, angiomyoma, leukemia, Zymbal gland carcinoma, pituitary adenoma, carcinoma, pituitary adenoma, mammary carcinoma and fibroma)	Froment et al. 1994
53	Rat (CD)	6 or 10 mo 5d/wk 6hr/d				250 (CEL: liver hemangiosarcoma, neoplastic nodules)	Hong et al. 1981
54	Mouse (A/J)	6 mo 5d/wk 6hr/d				50 (CEL: pulmonary adenoma)	Adkins et al. 1986
55	Mouse (B6C3F1)	6 mo 5d/wk 6hr/d				50 F (CEL: hemangiosarcoma of subcutis, peritoneum; mammary gland carcinoma)	Drew et al. 1983
56	Mouse (CD-1)	6 mo 5d/wk 6hr/d				50 F (CEL: hemangiosarcoma of skin, peritoneum; mammary gland carcinoma; lung carcinoma)	Drew et al. 1983
57	Mouse (CD-1)	1,3,6 mo 5d/wk 6hr/d				50 F (CEL: mammary gland adenocarcinoma/ carcinoma)	Hong et al. 1981

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)			LOAEL (effect) Serious (ppm)		Reference
58	Mouse (Swiss)	30 wk 5d/wk 4hr/d							50	(CEL: liver angiosarcoma and angioma)	Maltoni et al. 1981
59	Mouse (CD-1)	4 wk 5d/wk 6hr/d							100 M	(CEL: lung alveogenic tumors)	Suzuki 1983
60	Hamster (Golden Syrian)	6 mo 5d/wk 6hr/d							200 F	(CEL: liver hemangiosarcoma; skin hemangiosarcoma, spleen hemangiosarcoma; mammary gland carcinoma)	Drew et al. 1983
61	Hamster (Golden Syrian)	30 wk 5d/wk 4hr/d							500 M	(CEL: liver angiosarcoma)	Maltoni et al. 1981
CHRONIC EXPOSURE											
Systemic											
62	Rat (Wistar)	12 mo 6d/wk 6hr/d	Hepatic	100	M	3000	M	(increased liver weight)			Bi et al. 1985
			Renal	10	M	100	M	(increased kidney weight)			
			Bd Wt	10	M	100	M	(14% decrease in body weight)			
Reproductive											
63	Rat (Wistar)	12 mo 6d/wk 6hr/d		10	M				100 M	(testicular necrosis)	Bi et al. 1985

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
	Cancer						
64	Rat (Wistar)	12 mo 6d/wk 6hr/d				100 M (CEL: liver angiosarcoma; lung angiosarcoma)	Bi et al. 1985
65	Rat (Fischer- 344)	12, 18, 24 mo 5d/wk 6hr/d				100 F (CEL: hepatic hemangiosarcoma, hepatocellular carcinoma, neoplastic nodules; mammary gland fibroadenoma and adenocarcinoma)	Drew et al. 1983
66	Rat (CD)	1-12 mo 5d/wk 6hr/d				250 F (CEL: hepatic hemangiosarcoma)	Lee et al. 1978
67	Rat (Sprague-Dawley)	52 wk 5d/wk 4hr/d				5 F (CEL: mammary gland carcinoma)	Maltoni et al. 1981
68	Mouse (B6C3F1)	12 mo 5d/wk 6hr/d				50 F (CEL: hemangiosarcoma of peritoneum, subcutis; mammary gland carcinoma)	Drew et al. 1983
69	Mouse (Swiss CD-1)	12, 18 mo 5d/wk 6hr/d				50 F (CEL: lung; hemangiosarcoma of peritoneum, subcutis; mammary gland carcinoma)	Drew et al. 1983

TABLE 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
70	Mouse (CD-1)	1-12 mo 5d/wk 6hr/d				50 B (CEL: hepatic hemangiosarcoma; bronchiolo-alveolar adenoma; malignant lymphoma) 50 F (CEL: mammary gland adenoma and adenocarcinoma)	Lee et al. 1977a, Lee et al. 1978
71	Hamster (Golden Syrian)	12, 18, 24 mo 5d/wk 6hr/d				200 F (CEL: liver hemangiosarcoma; skin carcinoma, hemangiosarcoma; spleen hemangiosarcoma; mammary gland carcinoma; stomach adenoma)	Drew et al. 1983

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an acute-duration inhalation Minimal Risk Level (MRL) of 0.5 ppm. NOAEL converted to a Human Equivalent Concentration (HEC) before applying uncertainty factors. MRL obtained by dividing the $NOAEL_{HEC}$ by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive an intermediate-duration inhalation MRL of 0.03 ppm. LOAEL converted to an HEC before applying uncertainty factors. MRL obtained by dividing the $NOAEL_{HEC}$ by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

AKT = alpha-ketoglutarate transaminase; B = both; Bd Wt = body weight; Cardio = cardiovascular; CEL = Cancer Effect Level; d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gd = gestation days(s); Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphor = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; SDH = sorbitol dehydrogenase; wk = week(s); x = time(s)

Figure 2-1. Levels of Significant Exposure to Vinyl Chloride – Inhalation

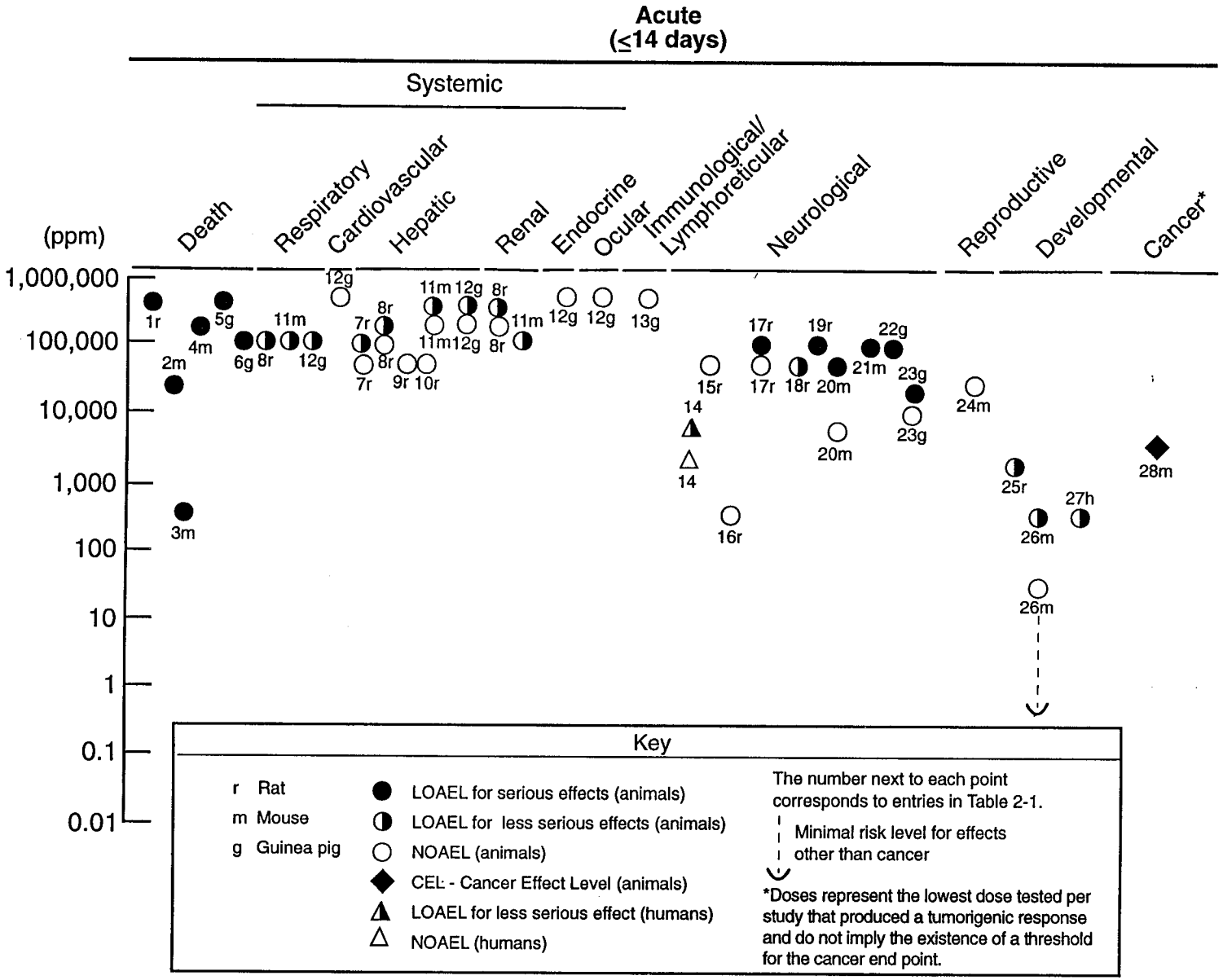


Figure 2-1. Levels of Significant Exposure to Vinyl Chloride – Inhalation (continued)

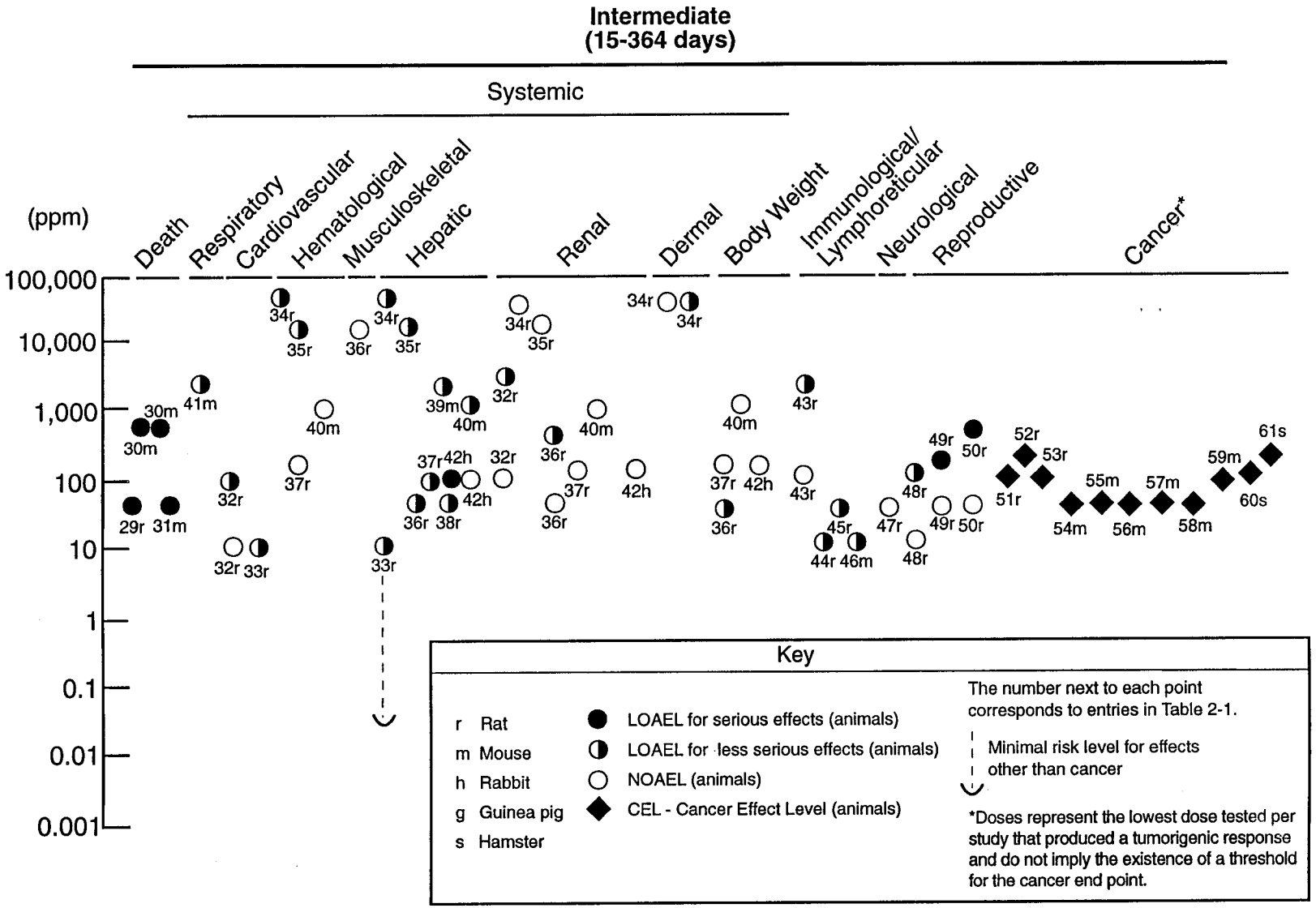
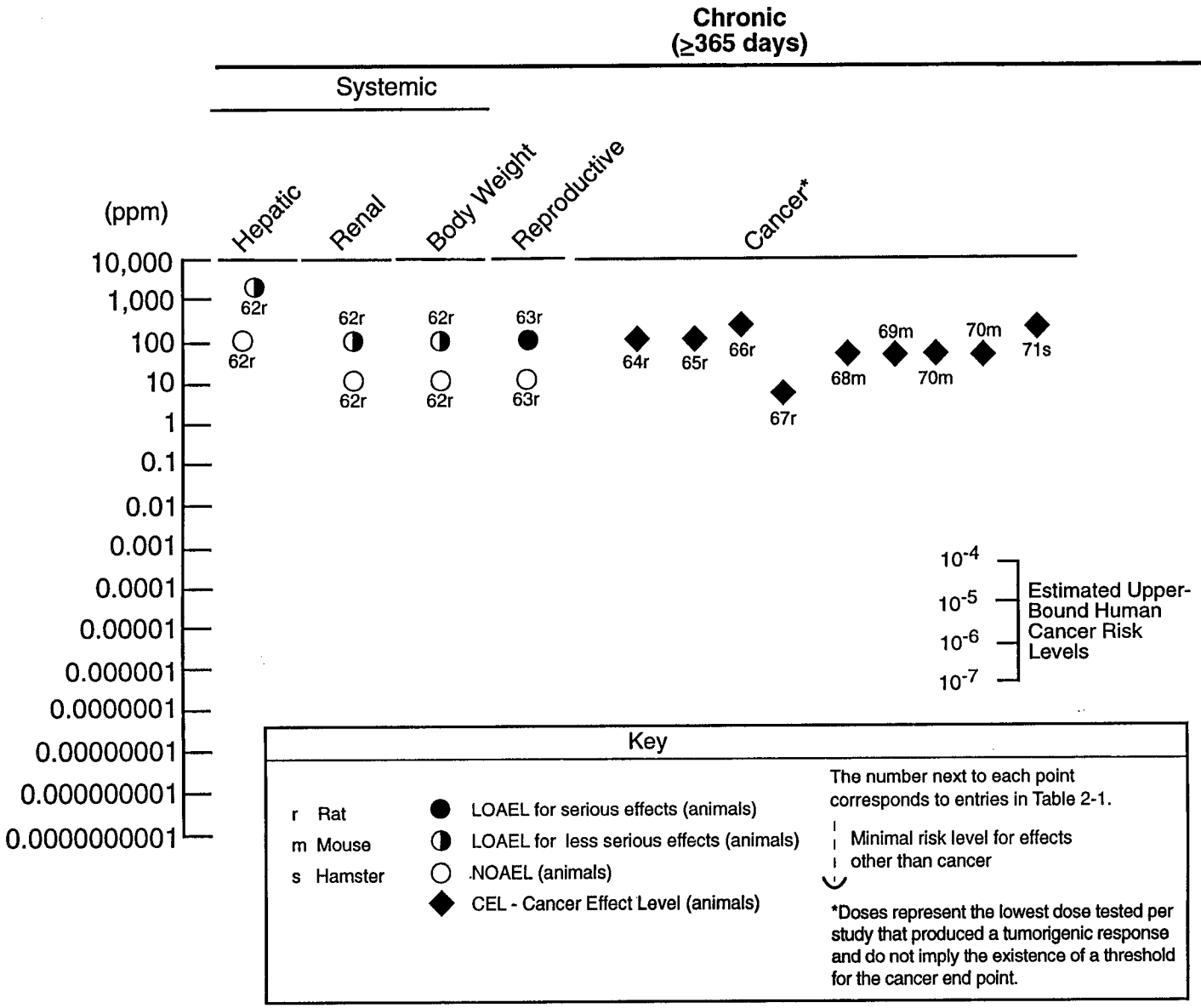


Figure 2-1. Levels of Significant Exposure to Vinyl Chloride – Inhalation (continued)



to be intensely hyperemic, and some desquamation of the alveolar epithelium had occurred (Danziger 1960). Reports regarding respiratory effects in workers who are occupationally exposed to vinyl chloride are contradictory. Several epidemiologic studies found no increased incidence of respiratory disease among vinyl chloride workers (Gamble et al. 1976; Laplanche et al. 1987, 1992; NIOSH 1977), but several other epidemiologic surveys and case reports found evidence of pulmonary damage. The adverse respiratory effects reported in these studies include increased incidence of emphysema (Suciu et al. 1975; Wong et al. 1991), decreased respiratory volume and vital capacity, respiratory insufficiency (Suciu et al. 1975), decreased respiratory oxygen and carbon dioxide transfer (Lloyd et al. 1984), pulmonary fibrosis of the linear type (Suciu et al. 1975), abnormal chest x-rays (Lilis et al. 1975, 1976), and dyspnea (Walker 1976). Interpretation of many of these results is confounded by the inclusion of smokers among those exposed to vinyl chloride and the concurrent exposure of many vinyl chloride workers to PVC resin dust, which is known to cause respiratory lesions (Mastrangelo et al. 1979).

Brief inhalation of high concentrations of vinyl chloride caused respiratory inflammation in a variety of animals. A 30minute exposure of guinea pigs, mice, and rats to 100,000 ppm of vinyl chloride produced slight hyperemia in all three species (Mastromatteo et al. 1960). Exposure to higher concentrations (200,000 ppm and 300,000 ppm) caused increased congestion, edema, and at the highest concentrations, pulmonary hemorrhages in all three species (Mastromatteo et al. 1960). Tracheal epithelium was also absent in one guinea pig exposed to 400,000 ppm for 30 minutes (Mastromatteo et al. 1960). Edema and congestion of the lungs of rats were also observed following a 2-hour exposure to 150,000 ppm (Lester et al. 1963).

Histopathologic examination of mice exposed to 2,500 ppm vinyl chloride for 5 hours per day, 5 days per week, for 5-6 months revealed proliferation and hypertrophy of the bronchiolar epithelium, hyperplasia of the alveolar epithelium, hypersecretion of mucin (Suzuki 1978, 1980, 1981), increased endoplasmic reticulum and free ribosomes in Clara cells, and mobilization of alveolar macrophages (Suzuki 1980). These changes were observed irrespective of the recovery period (2 or 37 days) indicating that they were not readily reversible. However, these studies were severely limited by the small number of animals tested and the absence of a statistical analysis.

Chronic exposure of rats to 5,000 ppm for 7 hours per day, 5 days per week, for 12 months produced hyperplasia of the olfactory epithelium, increased cellularity of the interalveolar septa of the lungs, and

an increased incidence of pulmonary hemorrhages (Feron and Kroes 1979). Interstitial pneumonia and hemorrhagic lungs were observed in rats exposed to 30,000 ppm of vinyl chloride for 4 hours per day, 5 days per week, for 12 months (Viola et al. 1971). However, the statistical significance of the findings in the studies by Feron and Kroes (1979) and Viola et al. (1971) is unknown.

Cardiovascular Effects. Occupational exposure to vinyl chloride has been associated with the development of Raynaud's phenomenon, a condition in which the fingers blanch and become numb with discomfort upon exposure to the cold. This condition has been reported most frequently among workers who cleaned the reactor tanks, a job which reportedly exposed workers to very high levels of vinyl chloride. It has also been reported in a worker exposed once to a vinyl chloride vapor leak (Ostlere et al. 1992). Although only a small percentage of vinyl chloride workers develop Raynaud's phenomenon (Laplanche et al. 1987, 1992; Lilis et al. 1975; Marsteller et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976), the incidence is significantly higher than in unexposed workers (Laplanche et al. 1987, 1992). Investigation of the peripheral circulation of workers afflicted with Raynaud's phenomenon has revealed thickening of the walls of the digital arteries (Harris and Adams 1967), narrowing of the arterial lumen (Veltman et al. 1975), vascular occlusions (Walker 1976), arterial occlusions (Preston et al. 1976; Veltman et al. 1975), tortuosity (Preston et al. 1976), hypervascularity (Preston et al. 1976), inflammatory infiltration of the arterioles (Magnavita et al. 1986), deposition of immune products along the vascular endothelium (Ward 1976), vasomotor impairment (Suciu et al. 1963), and impaired capillary microcirculation (Magnavita et al. 1986; Maricq et al. 1976). Three reports indicate that upon removal from exposure, Raynaud's phenomenon gradually disappears (Freudiger et al. 1988; Suciu et al. 1963, 1975). For further discussion of Raynaud's phenomenon, see Immunological/Lymphoreticular Effects (Section 2.2.1.3).

Splenomegaly, with evidence of portal hypertension (dilated peritoneal veins and esophageal varices), has been reported by investigators studying the effects of vinyl chloride exposure (Marsteller et al. 1975). In addition, hypertension among vinyl chloride workers (NIOSH 1977; Suciu et al. 1975) and significantly increased mortality due to cardiovascular and cerebrovascular disease (Byren et al. 1976) have been reported.

Investigators studying the anesthetic properties of vinyl chloride in dogs have observed that doses producing anesthesia (100,000 ppm, Oster et al. 1947; 150,000-900,000 ppm, Carr et al. 1949) also caused cardiac arrhythmias. Arrhythmias were characterized by intermittent tachycardia,

extraventricular systoles, vagal beats, ventricular fibrillation, and atrioventricular block. However, the statistical significance of these effects was not reported. No histopathological changes in the heart were noted in guinea pigs exposed to 400,000 ppm of vinyl chloride for 30 minutes (Mastromatteo et al. 1960).

A study by Bi et al. (1985) demonstrated an increase in the relative heart weight at concentrations of vinyl chloride as low as 10 ppm when administered to male rats for 6 hours per day, 6 days per week, for 6 months. Heart weight was also increased after 3 months in rats exposed to 100 ppm under this regimen (Bi et al. 1985). Chronic exposure of rats to 5,000 ppm vinyl chloride 7 hours per day, 5 days per week, for 1 year resulted in increases in areas of myodegeneration in the heart and thickening of the walls of arteries (Feron and Kroes 1979). However, the statistical significance of this effect was not reported. Exposure of rats to 30,000 ppm of vinyl chloride for 4 hours per day, 5 days per week, for 1 year also produced thickening of the walls of small arterial vessels. The thickening was characterized by a proliferation of the endothelium. In some vessels, the thickening was severe enough to cause blockage of the lumen (Viola 1970).

Gastrointestinal Effects. Approximately 32% of the vinyl chloride workers examined by Lilis et al. (1975) reported a history of "gastritis, ulcers (gastric and duodenal) and upper gastrointestinal bleeding." Because these subjects were not compared to workers who had not been exposed to vinyl chloride, the significance of these findings is unknown. Other symptoms reported by vinyl chloride workers included nausea, abdominal distension, and heartburn. Loss of appetite and nausea have been reported in Singapore workers exposed to l-21 ppm vinyl chloride (Ho et al. 1991). However, these workers were selected on the basis of liver dysfunction.

No studies were located regarding gastrointestinal effects in animals following inhalation exposure to vinyl chloride.

Hematological Effects. Blood tests performed at autopsy of two workers whose deaths were believed to be due to exposure to extremely high levels of vinyl chloride revealed that blood clotting did not occur (Danziger 1960). Slight-to-severe thrombocytopenia in workers occupationally exposed to vinyl chloride was reported in several studies (Marsteller et al. 1975; Micu et al. 1985; Veltman et al. 1975), but Lilis et al. (1975) found no increased incidence of thrombocytopenia in vinyl chloride workers. A prospective study of female workers exposed to vinyl chloride at levels ranging from 0.2

to 130.7 ppm showed that the exposed workers had a significantly lower number of platelets than the nonexposed controls during the early part of their pregnancies (weeks S-10) but that this effect abated by the end of the pregnancy (34-38 weeks) following a period free from exposure (Bao et al. 1988). Splenomegaly was reported in a number of studies (Ho et al. 1991; Marsteller et al. 1975; Popper and Thomas 1975; Suciu et al. 1963; Veltman et al. 1975). Thrombocytopenia was found in patients who both did and did not present with splenomegaly (Veltman et al. 1975). Increased levels of two plasma proteins (a,- and q-globulin) were reported in studies examining the effects of occupational exposure to vinyl chloride (Harris and Adams 1967; Suciu et al. 1975).

A brief (30-minute) exposure of guinea pigs to 400,000 ppm vinyl chloride resulted in a failure of the blood to clot in the animals that died during the exposure (Mastromatteo et al. 1960). Mice that were exposed to 5,000 ppm (6 days, 4 hours/day) or 10,000 ppm (5 days, 4 hours/day) showed an increased emergence of basophilic stippled erythrocytes (Kudo et al. 1990). This effect was also noted in mice that were exposed for 10 weeks to 50 ppm intermittently (4-5 days/week, 4 hours/day) or to 30-40 ppm continuously for 62 days (Kudo et al. 1990). Exposure of dogs and rats to 200 ppm, 7 hours per day, 5 days per week, for 6 months had no effect on hematologic values (Torkelson et al. 1961). Also, an g-week exposure of mice to 11,000 ppm for 6 hours per day, 5 days per week had no effect on erythrocyte or leukocyte counts (Sharma and Gehring 1979). Exposure of rats to either 50,000 ppm for 8 hours per day for 19 consecutive days or 20,000 ppm for 8 hours per day, 5 days per week, for 92 days resulted in a decrease in white cells (Lester et al. 1963). Exposure of rats to 5,000 ppm vinyl chloride for 7 hours per day, 5 days per week, for 1 year caused slightly increased hematopoiesis in the spleen (Feron and Kroes 1979). The statistical significance of these results was not provided. Blood clotting time was decreased in rats exposed to 5,000 ppm for 1 year, but the statistical significance of these effects was not reported (Feron et al. 1979a).

Musculoskeletal Effects. Acroosteolysis, or resorption of the terminal phalanges of the finger, was observed in a small percentage of workers occupationally exposed to vinyl chloride (Dinman et al. 1971; Lilis et al. 1975; Marsteller et al. 1975; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967). As with Raynaud's phenomenon, acroosteolysis was reported predominantly among polymerization tank cleaners. Bone lesions were most often confIned to the terminal phalanges of the fingers, but in a few cases the bones of the toes (Harris and Adams 1967), feet (Preston et al. 1976), sacroiliac joint (Harris and Adams 1967), and arms, legs, pelvis, and mandible (Preston et al. 1976) were also involved. Development of acroosteolysis was most often preceded by Raynaud's phenomenon

(Dinman et al. 1971; Freudiger et al. 1988; Harris and Adams 1967; Magnavita et al. 1986; Markowitz et al. 1972; Preston et al. 1976; Sakabe 197.5; Veltman et al. 1975; Wilson et al. 1967). In two reports, bone resorption was observed to progress despite discontinuation of exposure (Markowitz et al. 1972; Preston et al. 1976). However, in two other reports, improvement was observed after exposure ceased (Veltman et al. 1975; Wilson et al. 1967). Joint pain was also reported by Lilis et al. (1975).

Although Sokal et al. (1980) found no alterations in the bones of male rats exposed to 20,000 ppm for 5 hours per day, 5 days per week, for 10 months, Viola (1970) observed skeletal changes in the bones of rats exposed to 30,000 ppm for 4 hours per day, 5 days per week, for 12 months. The statistical significance of these effects was not reported and only one dose was tested.

Hepatic Effects. Throughout the early years of the use of vinyl chloride, workers experienced only a minimal degree of functional hepatic abnormalities. However, when it became apparent in the early 1970s that angiosarcoma of the liver was associated with long-term vinyl chloride exposure, an intensive effort was initiated by a number of investigators to characterize the hepatic effects of vinyl chloride. These studies revealed characteristic hepatic lesions produced by vinyl chloride exposure (Berk et al. 1975; Falk et al. 1974; Gedigke et al. 1975; Ho et al. 1991; Jones and Smith 1982; Lilis et al. 1975; Liss et al. 1985; Marsteller et al. 1975; NIOSH 1977; Popper and Thomas 1975; Suciu et al. 1975; Tamburro et al. 1984; Vihko et al. 1984). The incidence and severity of the effects correlated well with the duration of exposure (Gedigke et al. 1975; Lilis et al. 1975; NIOSH 1977). A further description of hepatic angiosarcoma may be found in Section 2.2.1.8.

Routine noninvasive techniques revealed hepatomegaly in a limited number of workers (1437%) (Ho et al. 1991; Lilis et al. 1975; Marsteller et al. 1975; NIOSH 1977; Suciu et al. 1963, 1975). However, when peritoneoscopy was performed or biopsies were obtained from exposed workers, Marsteller et al. (1975) found a much higher prevalence of hepatic abnormalities. Only 37% of the workers studied by Marsteller et al. (1975) were diagnosed with hepatomegaly, but peritoneoscopy revealed a 50% incidence of granular changes in the liver surface and an 86% incidence of capsular fibrosis with increased numbers of capsular vessels. Histopathological examination of the biopsied tissue from these workers revealed an 80% incidence of collagenization of the sinusoidal walls, a 90% incidence of proliferation of cells lining the sinusoids, a 30% incidence of septal fibrosis, and degeneration of hepatocytes (incidence not specified). A number of other investigators observed similar changes in liver tissues obtained from workers exposed to vinyl chloride (Falk et al. 1974; Gedigke et al. 1975;

Popper and Thomas 1975; Tamburro et al. 1984). Based on these observations, a profile of vinyl chloride-induced liver damage was compiled and includes the following features: hypertrophy and hyperplasia of hepatocytes, activation and hyperplasia of sinusoidal lining cells; fibrosis of the portal tracts and the septa and intralobular perisinusoidal regions, sinusoidal dilation, and focal areas of hepatocellular degeneration. This pattern of changes was observed to be highly unusual and was similar to the hepatic changes produced by arsenic (Gedigke et al. 1975). In addition, the degenerative changes in hepatocytes appeared to be less severe when biopsy material was obtained from workers who had not been exposed to vinyl chloride recently. However, sinusoidal changes were not influenced by the length of time since the last exposure (Gedigke et al. 1975).

One possible reason that the hepatotoxic effects of vinyl chloride went undetected for many years was the lack of sensitivity of standard biochemical liver function tests to detect the liver injury produced by vinyl chloride (Berk et al. 1975; Marsteller et al. 1975; Tamburro et al. 1984; Vihko et al. 1984). For example, the values obtained in several standard biochemical liver function tests (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyltranspeptidase) from workers with biopsy evidence of vinyl chloride-associated liver damage were not significantly higher than those from unexposed controls (Liss et al. 1985). Gamma-glutamyl transferase levels were significantly higher (pcO.01) in workers exposed to vinyl chloride at TWA exposure concentrations of >lO ppm compared to workers at lower exposure concentrations (Du et al. 1995). Workers exposed to lower levels of vinyl chloride had gamma-glutamyl transferase levels that were within the normal range (Hensyl 1990). Serum bile acids (Berk et al. 1975; Liss et al. 1985) and/or indocyanine green clearance (Liss et al. 1985; Tamburro et al. 1984) correlated with liver injury. Furthermore, investigators have shown that levels of chenodeoxycholic acid (a serum bile acid) in asymptomatic vinyl chloride workers were elevated when compared to the 95% interval of values from a healthy reference population (Vihko et al. 1984).

Brief exposure of animals to extremely high concentrations of vinyl chloride has been shown to cause hepatic damage. For example, acute exposure (30 minutes) of guinea pigs and mice to 300,000 ppm of vinyl chloride caused liver congestion or severe fatty degeneration while 200,000 ppm caused fatty infiltration in rats (Mastromatteo et al. 1960). Exposure to 100,000 ppm for 6 hours caused centrilobular vacuolization and slightly increased alanine serum a-ketoglutarate transaminase activity in rats (Jaeger et al. 1974). However, exposure of rats to 50,000 ppm for 6 hours produced no observable effects on the liver (Reynolds et al. 1975a, 1975b). In contrast, a single-concentration

study in which pregnant rats were continuously exposed to 1,500 ppm for 7-9 days during either the first or second trimester of pregnancy resulted in an increase in the liver-to-body-weight ratio (Ungvary et al. 1978). Interestingly, a single l-hour exposure of mice to 500, 5,000, or 50,000 ppm of vinyl chloride, followed by an 1%month observation period, resulted in an increased incidence of hepatocellular hypertrophy in these animals at terminal sacrifice (Hehir et al. 1981). The hypertrophy was not dose dependent; thus, the significance of this effect is uncertain.

In studies with longer durations of exposure, lower concentrations of vinyl chloride have produced hepatic toxicity. Symptoms of hepatotoxicity that have been observed in rats have included hepatocellular degeneration (Sokal et al. 1980; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980), swelling of hepatocytes with compression of sinusoids (Lester et al. 1963), dilation of the rough endoplasmic reticulum (Du et al. 1979), proliferation (Sokal et al. 1980) or hypertrophy (Wisniewska-Knypl et al. 1980) of smooth endoplasmic reticulum, changes in metabolic enzyme activities (Du et al. 1979; Wisniewska-Knypl et al. 1980), proliferation of reticulocytes (Sokal et al. 1980), and an increased liver-to-body-weight ratio (Bi et al. 1985; Lester et al. 1963; Sokal et al. 1980; Torkelson et al. 1961). For example, exposure of rats to 500 ppm for 7 hours per day, 5 days per week, for 4.5 months resulted in an increase in liver-to-body-weight ratio and granular degeneration (Torkelson et al. 1961). An increased liver-to-body-weight ratio was also found in rats exposed to 100 ppm vinyl chloride for 7 hours per day, 5 days per week, for 6 months (Torkelson et al. 1961). Relative liver weight was decreased in mice exposed to 1,000 ppm vinyl chloride for 6 hours per day, five days per week, for 8 weeks (Sharma and Gehring 1979). Exposure of rats to 500 ppm for 5 hours per day, 5 days per week, for 10 months caused swelling of hepatocytes and proliferation of reticuloendothelial cells, increased liver weight, and cellular degeneration; at 50 ppm, small lipid droplets and proliferation of smooth endoplasmic reticulum were noted (Sokal et al. 1980). Histopathological examination of rats exposed to either 50,000 ppm vinyl chloride for 8 hours per day for 19 consecutive days or 20,000 ppm vinyl chloride for 8 hours per day, 5 days per week, for 92 days showed hepatocellular hypertrophy, vacuolization, and sinusoidal compression (Lester et al. 1963). Mice exposed to 2,500 ppm vinyl chloride 5 hours per day, 5 days per week, for up to 6 months showed histopathological changes in the liver that included hyperplasia of hepatocytes and activated sinusoidal cells (Schaffner 1978). Centrilobular necrosis and degeneration were noted in rabbits exposed to 200 ppm vinyl chloride 7 hours per day, 5 days per week, for 6 months but not at 100 ppm vinyl chloride in this regimen (Torkelson et al. 1961). Also, exposure of rats to 50 ppm for 5 hours per day, 5 days per week, for 10 months produced fatty degeneration and proliferation of the smooth

endoplasmic reticulum (Wisniewska-Knypl et al. 1980). The liver-to-body-weight ratio was shown to be increased in male rats exposed to 3,000 ppm but not 100 ppm, vinyl chloride for 6 hours per day, 5 days per week, for 12 months (Bi et al. 1985). Significantly increased liver-to-body-weight ratio was also observed in rats exposed to concentrations of vinyl chloride as low as 10 ppm for 6 hours per day, 6 days per week, for 6 months (Bi et al. 1985). Based on this value, an intermediate-duration MRL of 0.03 ppm was calculated as described in the footnote in Table 2-l.

The relative NOAELs for a variety of species following a 6-month exposure to vinyl chloride indicated that mice and rats were the most sensitive (NOAEL = 50 ppm), rabbits were the next most sensitive (NOAEL = 100 ppm), and dogs and guinea pigs were the least sensitive (NOAEL > 200 ppm) (Torkelson et al. 1961).

Popper et al. (1981) compared histopathological findings from sections of liver from mice and rats exposed by Maltoni and LeFemine (1975) with the liver biopsy material obtained from vinyl chloride workers. Hyperplasia and hypertrophy of hepatocytes and/or sinusoidal cells, with areas of sinusoidal dilation, were observed in both humans and rodents. The major difference between the species was the greater degree of fibrosis, seen as reticulin deposition and collagen formation, in the livers of humans. Also, inflammatory cells were present in the livers of humans but not of rodents.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to vinyl chloride.

Acute exposure of mice and rats to 300,000 ppm of vinyl chloride for 30 minutes resulted in kidney congestion (Mastromatteo et al. 1960). Also, the kidneys of one mouse out of five exposed to either 100,000 or 200,000 ppm of vinyl chloride for 30 minutes showed degenerative changes (Mastromatteo et al. 1960). Exposure of rats to 50,000 ppm for 8 hours per day for 19 consecutive days or 20,000 ppm for 8 hours per day, 5 days per week, for 92 days caused no adverse effects on the kidneys (Lester et al. 1963). However, exposures of male rats to 3,000 ppm for 6 hours per day, 6 days per week, for 3 months caused the kidney-to-body-weight ratio to increase (Bi et al. 1985). After a 6-month observation period, there was also an increased kidney-to-body-weight ratio noted in the male rats exposed to 100 ppm vinyl chloride for 6 hours per day, 6 days per week, for 12 months; no effect was noted at 10 ppm (Bi et al. 1985). Relative kidney weight was increased in male rats exposed to 500 ppm vinyl chloride for 5 hours per day, 5 days per week, for PO months, although no

histopathological changes in the kidney were noted (Sokal et al. 1980). No changes in kidney weight were reported when mice were exposed to 1,000 ppm vinyl chloride for 8 weeks, 5 days per week, 6 hours per day (Sharma and Gehring 1979). Urinalysis values were within normal limits in rats and rabbits exposed to 200 ppm vinyl chloride for up to 7 hours per day, 5 days per week, for 6 months (Torkelson et al. 1961). One year of exposure to 5,000 ppm vinyl chloride for 7 hours per day, 5 days per week caused increased kidney-to-body-weight ratio (Feron et al. 1979a) and tubular nephrosis in rats (Feron and Kroes 1979). However, the statistical significance of these findings was not provided in the study.

Endocrine Effects. A study of workers exposed to vinyl chloride in PVC manufacturing plants reported that most workers who presented with scleroderma were shown to have thyroid insufficiency (Suciu et al. 1963).

No histopathological effects on the adrenals were reported in guinea pigs exposed to 400,000 ppm for 30 minutes (Mastromatteo et al. 1960). Rats exposed to 30,000 ppm vinyl chloride for 12 months, 5 days per week, 4 hours per day were found to have colloid goiter and markedly increased numbers of perifollicular cells (Viola 1970).

Dermal Effects. Occupational exposure to vinyl chloride was observed to cause scleroderma-like skin changes on the hands of a small percentage of exposed workers (Freudiger et al. 1988; Lilis et al. 1975; Marsteller et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976). The skin changes were characterized by a thickening of the skin (Lilis et al. 1975; Markowitz et al. 1972; Ostlere et al. 1992; Preston et al. 1976; Veltman et all. 1975; Walker 1976), decreased elasticity (Lilis et al. 1975), and slight edema (Lilis et al. 1975; Suciu et al. 1975) and were almost exclusively observed in exposed individuals who also suffered from Raynaud's phenomenon. Skin biopsies revealed increased collagen bundles in the subepiderrnal layer of the skin (Harris and Adams 1967; Markowitz et al. 1972; Ostlere et al. 1992; Veltman et al. 1975). Biochemical analyses by Jayson et al. (1976) demonstrated that a high rate of collagen synthesis was taking place in the affected skin. Most often the skin changes were confined to the hands and wrists, but Jayson et al. (1976) reported scleroderma-like skin changes on the hands, arms, chest, and face of one afflicted worker.

Skin changes were observed in rats exposed to 30,000 ppm for 12 months (Viola 1970). The skin of the paws of the exposed rats showed areas of hyperkeratosis, thickening of the epidermis, edema,

collagen dissociation, and fragmentation of the elastic reticulum. Interpretation of these results is limited by the absence of a statistical analysis and insufficient information on the treatment of control animals. Lester et al. (1963) reported that male rats exposed to 50,000 ppm vinyl chloride for 19 days, 8 hours per day had thin coats and scaly tails, while females exposed to the same concentration showed no effects. For further information regarding scleroderma-like responses to vinyl chloride exposure, see Cardiovascular Effects (Section 2.2.1.2) and Immunological and Lymphoreticular Effects (Section 2.2.1.3).

Ocular Effects. Ocular effects that have been reported after inhalation exposure are believed to have resulted from direct contact of the vinyl chloride vapor with the eyes and are discussed under Dermal Exposure (Section 2.2.3.2). No studies were located regarding ocular effects in humans that were related solely to the inhalation of vinyl chloride. No histopathological changes were noted in the eyes of guinea pigs exposed to 400,000 ppm vinyl chloride for 30 minutes (Mastromatteo et al. 1960).

Body Weight Effects. Several studies have reported that workers intoxicated by vinyl chloride experienced anorexia (Suciu et al. 1963, 1975).

No effects on body weight were noted in ICR mice exposed to either 10,000 ppm vinyl chloride for 5 days, 4 hours per day or to 5,000 ppm vinyl chloride for 6 days, 4 hours per day (Kudo et al. 1990). No consistent or dose-related differences in body weight were noted between control rats and rats exposed to up to 50,000 ppm for 1 hour or rats exposed to 500 ppm, 5 days per week, for 2 weeks (Hehir et al. 1981). However, statistical analysis was not performed. No changes in body weight were noted in rats or rabbits exposed to 200 ppm vinyl chloride for 6 months, 5 days per week, 7 hours per day (Torkelson et al. 1961) or in mice exposed to 1,000 ppm vinyl chloride for 8 weeks, 5 days per week, 6 hours per day (Sharma and Gehring 1979). Significant decreases were found in the body weight of rats exposed to 100 ppm vinyl chloride for 12 months, 6 hours per day, 6 days per week; these changes were not observed at 10 ppm (Bi et al. 1985). Significant decreases were also noted in mean body weights of rats exposed to 5,000 ppm vinyl chloride for 4-52 weeks, 5 days per week, 7 hours per day, but data were not quantified (Feron et al. 1979a). This study was limited since only one concentration was tested. Body weight was decreased ($p<0.05$) 10% in male rats exposed to 50 ppm vinyl chloride for 10 months, 5 hours per day, 5 days per week (Sokal et al. 1980). Maternal body weight gain was significantly decreased in mice exposed to 500 ppm for 7 hours per day during gestational days 6-15 (John et al. 1977).

2.2.1.3 Immunological and Lymphoreticular Effects

A number of studies have examined the immunologic profiles of workers occupationally exposed to vinyl chloride. Male workers exposed to vinyl chloride for an average of 8 years, with concentrations ranging from 1 to 300 ppm during sampling periods, were found to have significantly increased percentages of lymphocytes compared to controls (Fucic et al. 1995). Additionally, 75 out of these 100 workers showed disturbances of mitotic activity in these cells. A statistically significant increase in circulating immune complexes in workers exposed to vinyl chloride was observed when compared to levels in unexposed workers (Bogdanikowa and Zawilska 1984). The increase in circulating immune complexes was greatest in women and in those with duties involving exposure to relatively higher levels of vinyl chloride. Compared to controls, immunoglobulin G (IgG) levels were significantly increased in women exposed to the high levels of vinyl chloride in the same study.

Studies of workers who have developed “vinyl chloride disease,” a syndrome consisting of Raynaud’s phenomenon, acroosteolysis, joint and muscle pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes, indicate that this disease may have an immunologic basis. Sera obtained from patients with varying degrees of severity of symptoms of vinyl chloride disease demonstrate a close correlation between the disease severity and the extent of the immunologic abnormality (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward %976), although these symptoms have been reported without immunological findings (Black et al. 1986; Ostlere et al. 1992). The most frequent immunologic finding in workers with vinyl chloride disease is an increase in circulating immune complexes or cryoglobulinemia. In workers with the most severe clinical signs, there also are an increased incidence of B-cell proliferation, hyperimmunoglobulinemia (Ward 1976), cryoglobulinemia (Grainger et al. 1980), and complement activation (Grainger et al. 1980; Ward 1976). Evidence of a structurally altered IgG has been obtained, and it has been proposed that vinyl chloride (or a metabolite) binds to IgG (Grainger et al. 1980). Should such binding occur, the resulting complex may be the antigenic substance that triggers the immune reaction.

Based on the similarity of vinyl chloride disease and systemic sclerosis, which may be a genetically linked autoimmune disease, Black et al. (1983, 1986) examined the human lymphocyte antigen (HLA) phenotypes of patients with vinyl chloride disease. Many autoimmune diseases show statistically significant associations with certain HLA alleles. These authors found that when compared to unexposed controls or asymptomatic controls, workers with vinyl chloride disease had a significantly

greater incidence of possessing the HLA-DRS allele. Furthermore, among those with the disease, the severity of the symptoms was significantly related to the possession of the HLA-DR3 and B8 alleles. These authors concluded that susceptibility was increased in the presence of HLA-DR5 or a gene in linkage disequilibrium with it, and progression was favored by HLA-DR3 and B8.

Splenomegaly was reported in a number of studies (Ho et al. 1991; Marsteller et al. 1975; Popper and Thomas 1975; Suciu et al. 1963; Veltman et al. 1975). No histopathological changes were noted in the spleen or lymph nodes of guinea pigs exposed to 400,000 ppm vinyl chloride for 30 minutes (Mastromatteo et al. 1960). An increase in the relative spleen weight was observed in rats exposed to 50 ppm for 5 hours per day, 5 days per week, for 10 months (Sokal et al. 1980). Although no dose response was evident, increased relative spleen weight was also reported by Bi et al. (1985) when rats were exposed to either 10 ppm for 6 hours per day, 6 days per week, for 6 months or 3,000 ppm for 6 hours per day, 6 days per week, for 3 months. This effect was not observed at 100 ppm in the 3-month study (Bi et al. 1985).

The immunologic effects of vinyl chloride have been examined in mice (Sharma and Gehring 1979). Lymphocytes isolated from the spleens of mice exposed to concentrations as low as 10 ppm vinyl chloride for 4 weeks, 5 days per week, 6 hours per day had increased spontaneous and lectinstimulated transformation. This increase was not observed when lymphocytes from unexposed mice were cultured in the presence of vinyl chloride, indicating that a metabolite of vinyl chloride may be responsible for the increase.

The highest NOAEL value and all reliable LOAEL values for immunological effects in guinea pigs, mice, and rats exposed in acute- and intermediate-duration studies are recorded in Table 2-l and plotted in Figure 2-l. For further information on Raynaud’s syndrome and scleroderma-like responses to vinyl chloride, see Cardiovascular and Dermal Effects (Section 2.2.1.2).

2.2.1.4 Neurological Effects

Vinyl chloride was once considered for use as an inhalation anesthetic (ACGIH 1986). Investigators studying the effects of vinyl chloride exposure frequently report central nervous system symptoms that are consistent with the anesthetic properties of vinyl chloride. The most commonly reported central nervous system effects are ataxia or dizziness (Ho et al. 1991; Langauer-Lewowicka et al. 1983; Lilis

et al. 1975; Marsteller et al. 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975), drowsiness or fatigue (Langauer-Lewowicka et al. 1983; Spirtas et al. 1975; Suciu et al. 1963, 1975; Walker 1976), loss of consciousness (NIOSH 1977), and/or headache (Langauer-Lewowicka et al. 1983; Lilis et al. 1975; Marsteller et al. 1975; NIOSH 1977; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975). Other central nervous system effects that have been reported by vinyl chloride workers include euphoria and irritability (Suciu et al. 1963, 1975), visual and/or hearing disturbances (Marsteller et al. 1975), nausea (Marsteller et al. 1975; Spirtas et al. 1975), memory loss (Langauer-Lewowicka et al. 1983; Suciu et al. 1963, 1975), and nervousness and sleep disturbances (Langauer-Lewowicka et al. 1983; Suciu et al. 1963). Central nervous system tests revealed pyramidal signs and cerebellar disturbances in some exposed subjects (Langauer-Lewowicka et al. 1983); however, reliable estimates of exposure levels producing these effects were not available.

Exposure of volunteers to known levels of vinyl chloride has provided some indication of the levels of vinyl chloride associated with the effects noted above. Volunteers exposed to 25,000 ppm vinyl chloride for 3 minutes, in a single-dose study, reported experiencing dizziness, disorientation, and burning sensations in the feet during exposure (Patty et al. 1930). Recovery from these effects was rapid upon termination of exposure, but the subjects developed headaches. Exposure of volunteers to concentrations of vinyl chloride ranging from 4,000 to 20,000 ppm for 5 minutes twice a day in periods separated by 6 hours on 3 consecutive days was studied by Lester et al. (1963). No effects were noted at 4,000 ppm. However, at 8,000 ppm one of six subjects reported feeling dizzy. The incidence of dizziness increased as the concentration increased. Nausea was experienced at higher concentrations, and recovery from all effects was rapid upon termination of exposure. Headaches developed following exposure to 20,000 ppm.

Indications of an exposure-related peripheral neuropathy have been observed in a number of the occupational studies. A slight peripheral neuropathy, most severe in hands and feet, was diagnosed in 70% of the vinyl chloride workers examined in a study by Perticoni et al. (1986). The peripheral neuropathy was manifested as denervation-related fasciculations and fibrillations and increased duration and amplitude of motor unit potentials (indicating collateral sprouting). Similar effects were observed by Magnavita et al. (1986) in a case study of a vinyl chloride worker. Other peripheral nervous system symptoms have been reported by a number of investigators studying the effects of occupational exposure to vinyl chloride. The symptom most frequently reported was tingling (paresthesia) in the extremities (Lilis et al. 1975; Sakabe 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al.

1975; Walker 1976). Additional peripheral nervous system symptoms included numbness in the fingers (Lilis et al. 1975; Sakabe 1975), weakness (Langauer-Lewowicka et al. 1983; Suciu et al. 1963, 1975), depressed reflexes (NIOSH 1977), warmth in the extremities (Suciu et al. 1963, 1975), and pain in the fingers (Sakabe 1975). It is unclear whether some of these symptoms are associated with tissue anoxia due to vascular insufficiency, or whether they represent the direct toxic effects of vinyl chloride on peripheral nerves.

Acute exposure of a number of species to high levels of vinyl chloride has provided additional information on the characteristics of the central nervous system effects that are produced. Exposure of guinea pigs to 10,000 ppm for 8 hours (Patty et al. 1930) was observed to be without effects. Increasing the concentration to 25,000 ppm resulted in ataxia, which developed into unconsciousness during the 8-hour exposure period. As the concentration was increased, the development of unconsciousness was more rapid. At 100,000 ppm, Mastromatteo et al. (1960) observed the development of unconsciousness within 30 minutes. Mice experienced similar signs at approximately equivalent exposure levels. At 5,000 ppm, vinyl chloride was without effect during a l-hour exposure period. Increasing the concentration to 50,000 ppm caused ataxia and twitching (Hehir et al. 1981), and at 100,000 ppm for 30 minutes unconsciousness was produced, preceded by increased motor activity, incoordination, twitching, and tremors (Mastromatteo et al. 1960). Similar effects in rats were observed by Lester et al. (1963), Jaeger et al. (1974), and Mastromatteo et al. (1960). In contrast, in two reports using rats, exposure to 50,000 ppm for either 1 or 6 hours was without effect (Hehir et al. 1981; Jaeger et al. 1974). No effects were noted in rats exposed to 500 ppm vinyl chloride for 2 weeks (5 days per week, 1 hour per day) or in rats exposed to 50 ppm for 20 weeks (5 days per week, 1 hour per day) (Hehir et al. 1981). In addition, tolerance developed to the intoxicating effects of exposure to 50,000 ppm vinyl chloride after five or six g-hour exposures (Lester et al. 1963).

Chronic exposure of rats to high levels of vinyl chloride has produced damage to nervous tissue. Rats exposed to 30,000 ppm for 4 hours per day, 5 days per week, for 12 months in a single-concentration study were slightly soporific during exposures (Viola 1970; Viola et al. 1971). Following 10 months of exposure, the rats had decreased responses to external stimuli and disturbed equilibrium. Histopathological examination revealed diffuse degeneration of gray and white matter. Cerebellar degeneration in the Purkinje cell layer was pronounced. Also, peripheral nerve endings were surrounded and infiltrated with fibrous tissue (Viola 1970; Viola et al. 1971). Nonneoplastic lesions in

the brain were not noted in rats exposed to 5,000 ppm for 7 hours per day, 5 days per week, for 12 months in a single-concentration study by Feron and Kroes (1979).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species from acute- or intermediate-duration studies are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.5 Reproductive Effects

A number of case reports of workers occupationally exposed to vinyl chloride suggest that sexual performance may be affected by vinyl chloride. However, these studies are limited by the lack of quantification of exposure levels and possible concomitant exposures to other chemicals. Sexual impotence was reported by 24% of the workers examined by Suciu et al. (1975). Approximately 20% of the workers examined by Veltman et al. (1975) complained of potency troubles. A loss of libido in 35% and impotence and decreased androgen secretion in 8% of workers exposed at least once to very high levels of vinyl chloride were also reported by Walker (1976).

In retrospective and prospective studies by Bao et al. (1988), increased incidence and severity of elevated blood pressure and edema during pregnancy (preeclampsia) were found in female workers exposed to vinyl chloride when compared to unexposed workers. Company records indicated that exposure levels ranged from 3.9 to 89.3 ppm during the retrospective study and from 0.2 to 130.7 ppm during the prospective study. More detailed information regarding the exposure levels was not presented.

Although no studies were located that documented the effects of vinyl chloride on reproductive performance when both parental animals were exposed, two dominant lethal studies examined the reproductive performance of exposed males. A brief exposure (5 days, 6 hours per day) of mice to concentrations of vinyl chloride as high as 30,000 ppm had no effect on male fertility or pre- or postimplantation loss (Anderson et al. 1976). In contrast, exposure of male rats to concentrations as low as 250 ppm for 6 hours per day, 5 days per week, for 11 weeks caused a decrease in the ratio of pregnant to mated females, indicating a decrease in male fertility; this effect was not observed at 50 ppm (Short et al. 1977). These results are supported by two studies using rats in which adverse effects of vinyl chloride on the testes were observed (Bi et al. 1985; Sokal et al. 1980). Exposure of rats to 100 ppm for 6 hours per day, 6 days per week, for 12 months caused a significant increase in

the incidence of damage to the seminiferous tubules and depletion of spermatocytes (Bi et al. 1985). At the 6-month interim sacrifice, a significant decrease in testicular weight was also observed at 100 ppm. No effect on male reproductive organs was observed in this study at 10 ppm. A significant increase in damage to the spermatogenic epithelium and disorders of spermatogenesis were found with exposure to 500 ppm vinyl chloride for 5 hours per day, 5 days per week, for 10 months but was not observed after exposure to 50 ppm vinyl chloride (Sokal et al. 1980). No significant decrease in testicular weight was found in rats exposed to 500 ppm for 7 hours per day, 5 days per week, for 4.5 months or in dogs, rabbits, or guinea pigs exposed to 200 ppm for 7 hours per day, 5 days per week, for 6 months (Torkelson et al. 1961). However, the quality of this study is limited because of the small number of animals tested. Exposures involved up to 10 rats or guinea pigs of each sex, 3 rabbits of each sex, and 1 dog of each sex. No histopathological data on the testes of these animals were presented.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.1.6 Developmental Effects

Although evidence has been presented indicating that members of communities with nearby vinyl chloride polymerization facilities have significantly greater incidences of some forms of developmental toxicity, these studies failed to demonstrate a statistically significant correlation between the developmental toxicity and either parental occupation or proximity to the facility (Edmonds et al. 1978; Infante 1976; Rosenman et al. 1989; Theriault et al. 1983).

The pregnancy outcome of wives of workers employed at a vinyl chloride polymerization facility was compared to the pregnancy outcome of wives of a control group made up of unexposed rubber workers and PVC fabricators believed to be exposed to “very low” levels of vinyl chloride (Infante et al. 1976a, 1976b). Pregnancy outcomes were determined based on the responses given by fathers on a questionnaire. Infante et al. (1976a, 1976b) and NIOSH (1977) reported a significant excess of fetal loss in the group whose husbands had been exposed to vinyl chloride. The greatest difference occurred in wives of men under 30 years of age, where fetal loss was 5.3% for controls and 20.0% for exposed workers. However, this study has been severely criticized based on the conduct of the study and method of statistical analysis used (Hatch et al. 1981; Stallones 1987). Furthermore, Hatch et al.

(1981) and Stallones (1987) concluded that the study failed to demonstrate an association of parental exposure to vinyl chloride with increased fetal loss.

Additional work by Infante (1976) and Infante et al. (1976b) examined the occurrence of congenital malformations among populations exposed to emissions from PVC polymerization facilities. A statistically significant increase in birth defects was observed in three cities in which polymerization facilities were located when compared to statewide and countywide averages. The greatest increases were noted in malformations of the central nervous system, upper alimentary tract, and genital organs and in the incidence of club foot. However, this study has also been criticized based on the conduct and analyses used (Hatch et al. 1981; Stallones 1987). These authors concluded that the study failed to demonstrate an association between exposure to emissions and the prevalence of birth defects. Furthermore, another study that examined the incidence of malformations in one of the cities studied by Infante (1976) concluded that, although the city had statistically increased incidences of congenital malformations, no correlation existed with parental proximity to the polymerization plant or with parental employment at the plant (Edmonds et al. 1975). In fact, more parents of control infants worked at the plant or lived closer to the plant than parents of infants with central nervous system malformations.

Additional studies have also examined the prevalence of congenital malformations in populations exposed to emissions from polymerization facilities (Edmonds et al. 1978; Rosenman et al. 1989; Theriault et al. 1983). The incidence of central nervous system defects in a West Virginia county with a polymerization plant was compared to incidences in other regions in the United States with no known exposure to vinyl chloride (Edmonds et al. 1978). Although the rate of central nervous system defects in the West Virginia county exceeded that in control areas, no correlation was noted between the increased central nervous system defects and parental occupation or potential exposure based on proximity to the plant or prevailing wind patterns.

A significantly greater prevalence of birth defects was found in residents of a town with a polymerization facility than in three matched towns without potential for exposure to vinyl chloride (Theriault et al. 1983). The most commonly reported defects included those of the musculoskeletal, alimentary, urogenital, and central nervous systems. The incidences were observed to fluctuate with seasonal changes in emissions. However, no correlations were found between the presence of defects and proximity of the residence to the plant or parental occupation. Also, other industrial emissions

could not be eliminated as potential sources of the increased incidence of congenital malformations observed.

No significant increases in birth defects were observed in a community with two polymerization facilities, but odds ratios for central nervous system defects were found to correlate with the amount of emissions from the individual facilities and with the distance of the residences of affected parents from the facilities (Rosenman et al. 1989). However, this study was limited by the small sample size.

Pregnancy outcomes of mothers occupationally exposed to vinyl chloride for more than 1 year were compared to those of pregnant workers not exposed to vinyl chloride in retrospective and prospective studies (Bao et al. 1988). Company records indicated that exposure levels ranged from 3.9 to 89.3 ppm during the retrospective study and from 0.2 to 130.7 ppm during the prospective study. More detailed information regarding the exposure levels was not presented. The study authors concluded that exposure to vinyl chloride did not correlate with changes in sex ratio, birth weight or height, perinatal mortality, or the incidence of congenital abnormalities.

A number of inhalation studies have examined the effects of vinyl chloride exposure on pregnancy outcome in animals. Results of these studies indicate that vinyl chloride produces developmental effects at concentrations that are also toxic to maternal animals. John et al. (1977, 1981) exposed rats and rabbits to 0, 500, or 2,500 ppm and mice to 0, 50, or 500 ppm throughout the period of organogenesis. Separate control groups were used for each of the mice exposure concentrations. Mice were most sensitive to the effects of vinyl chloride. In mice exposed to 500 ppm, maternal toxicity was evidenced by decreased food consumption, decreased body weight gain, and increased mortality (John et al. 1977, 1981). Delayed ossification was noted in fetuses at 500 ppm. The only significant fetal effect observed at 50 ppm was an increase in crown-rump length. The biological significance of this effect is unknown. Based on this NOAEE of 50 ppm, an acute-duration MRL of 0.5 ppm was calculated as described in the footnote in Table 2-l. In rats, 500 ppm caused decreased maternal weight gain and fetal weight, increased crown-rump length, and vertebral lumbar spurs. Increasing the exposure level to 2,500 ppm was not associated with a dose-dependent increase in these effects. The only effects observed at 2,500 ppm were decreased maternal food consumption and, in fetuses, an increased incidence of dilated ureters. In rabbits exposed to 500 ppm, maternal animals had decreased food consumption, and fetal animals had delayed ossification. These effects were not observed in rabbits at 2,500 ppm. However, the number of animals that were tested at 2,500 ppm was much lower

than at 500 ppm (5 versus 20); thus no conclusions may be drawn as to the dose response of these effects.

Exposure of rats to either 0 or 1,500 ppm of vinyl chloride during the first, second, or third trimester of pregnancy was examined (Ungvary et al. 1978). In maternal animals, an increased liver-to-bodyweight ratio was observed in those exposed during the first and second trimesters, but no histopathologic alterations were found. A significant increase in resorptions was observed in animals exposed during the first trimester of pregnancy. Two central nervous system malformations (microphthalmia and anophthalmia) were observed in exposed fetuses but not in controls, but the incidence of these malformations did not reach statistical significance. This study is limited in that only a single concentration of vinyl chloride was tested, precluding conclusions as to the dose-response relationship of the effects observed.

The effects of exposure of rats to vinyl chloride throughout gestation were examined by Mirkova et al. (1978) and Sal'nikova and Kotsovskaya (1980). An unspecified number of pregnant rats were exposed to 0, 1.9, or 13.9 ppm for 4 hours per day for the 21 days of gestation. Fetuses were examined for abnormalities just prior to the end of gestation, and offspring were examined at 6 months postparturition (Sal'nikova and Kotsovskaya 1980). At 13.9 ppm, a decrease in maternal erythrocyte count was observed. At 1.9 and 13.9 ppm, fetuses had an increased incidence of hemorrhages, and at 13.9 ppm, increased edema. However, the affected organs were not specified. Rats examined at 6 months, following in utero exposure to 1.9 ppm, were found to have decreased hemoglobin and leukocytes and decreased organ weights (males: liver, kidney, spleen; females: lung, liver). In addition to these effects, exposure to 13.9 ppm in *utero* resulted in an increased hexanol sleep time and a decreased ability of the rats to orient themselves.

Continuous exposure of an unspecified number of rats throughout gestation to 2.4 ppm of vinyl chloride resulted in decreased fetal weight and increased early postimplantation loss, hematomas, and hydrocephaly with intracerebral hematoma. Weanling rats had hepatotoxic effects including decreased bile enzyme activity, decreased bile secretion, decreased cholic acid content, and increased hexobarbital sleep time. No histological data on the livers of pups, or information regarding maternal health, or statistical analyses of the data were presented (Mirkova et al. 1978). Also, both this study and the report by Sal'nikova and Kotsovskaya (1980) failed to provide information on the number of animals in each test group.

The highest NOAEL value and all reliable LOAEL values for developmental effects in mice, rats, and/or rabbits in acute-duration studies are recorded in Table 2-l and plotted in Figure 2-l. Discussion of transplacental carcinogenic effects or carcinogenic effects that occurred after postpartum exposure can be found in Section 2.2.1.8 (Cancer).

2.2.1.7 Genotoxic Effects

Genotoxicity studies of vinyl chloride in humans include a large number of assays for chromosomal aberrations in the cultured lymphocytes of occupationally exposed workers. Studies completed through the mid-1980s generally found a statistically significant increase in the frequency of chromosomal aberrations, usually of the chromatid type (i.e., affecting only one of the two strands formed upon deoxyribonucleic acid [DNA] replication) but also including some chromosomal-type defects such as inversions, rings, and translocations, which affect the entire chromosome. Workers exposed to vinyl chloride for an average of 15 years were shown to have elevated levels of micronuclei and chromosomal aberrations when compared to the unexposed controls (Garaj-Vrhovac et al. 1990). Micronuclei counts were also increased (pcO.001) in a group of 52 workers exposed to vinyl chloride levels of 1.3-16.7 ppm compared to those of controls, but these increases were not observed in workers exposed to 0.3-7.3 ppm (Sinues et al. 1991). Increased sister chromatid exchanges have also been reported in occupationally exposed workers (Fucic et al. 1992, 1995; Kucerova et al. 1979; Sinues et al. 1991; Zhao et al. 1994). Sister chromatid exchange frequencies were increased (<0.001) compared to those of the controls at 0.003-7.3 ppm vinyl chloride (Sinues et al. 1991). A study examined 37 exposed workers and from 16 to 32 unexposed controls twice at intervals of from 2 to 2.5 years (Hansteen et al. 1978). The exposure level during the time of the first sampling was measured at 25 ppm, and there was a statistically significant increase in aberrations among the exposed workers. At the subsequent examination, exposure levels had dropped to 1 ppm and the chromosomal aberrations had returned to normal. There were no statistical differences between exposed subjects and controls in the percentage of chromosomal aberrations.

It was reported that the increase of chromosome aberrations observed in workers exposed to 50 ppm returned to normal within 42 months when the cohort was sampled after exposure levels had been reduced to less than 5 ppm (Anderson et al. 1980). A positive correlation between frequency of chromosomal aberrations and length of exposure and history of exposure to excursion levels (up to 2,000 ppm) was reported by Purchase et al. (1978), who examined a cohort of 57 vinyl chloride

workers, 19 on-site controls, and 5 off-site controls. The exposures for this cohort ranged from 1,000 ppm between 1945 and 1955 to 5 ppm since 1975. These authors also reported an effect on chromosomal aberrations from smoking. However, the reversibility of clastogenic effects was not seen in another study of 12 current and 3 retired plastics industry workers who had been exposed to vinyl chloride while employed for 1.5-35 years (Fucic et al. 1992). Sister chromatid exchange frequencies were significantly higher in workers exposed to concentrations up to 2,000 ppm than in the controls. These findings showed no significant decrease in sister chromatid exchange frequencies from 8 days to 10 years after exposure (Fucic et al. 1992).

Other papers on human subjects have focused on specific mechanisms involved in the clastogenic effects of vinyl chloride. A cohort of 67 workers exposed to approximately 5 ppm for an average of 15 years was reported to have a nonrandom distribution of chromatid and bichromatid breaks (Fucic et al. 1990). The most frequently affected areas of the genome were the terminal segments of the A, B, and C group chromosomes, suggesting that vinyl chloride or its metabolites interact more frequently with specific sites along the chromosome than would be expected. The study authors presented no correlation with particular fragile sites (gene sequences more prone to breakage than normal) or oncogene locations known to occur at these terminal segments. The implication is that the carcinogenicity of vinyl chloride could be at least partially explained by its nonrandom interaction with particular genes. These workers were also periodically exposed to 2,000 ppm for short periods. No specific information was given as to the frequency or duration of these events.

Male workers (n=20) who had been employed for 2-14 years at a vinyl chloride polymerization plant exposed to concentrations of vinyl chloride of 1 ppm (with occasional peaks of 300 ppm) underwent cytogenetic testing (Fucic et al. 1995). The test results were compared to those from 20 unexposed control men. Exposed individuals had higher percentages of chromosome aberrations, primarily chromatid breaks. Sister chromatid exchange frequencies were also increased in exposed workers (4-22 per cell) compared to controls (4-7 per cell). Significant changes in mitotic activity were noted among exposed workers; values for second mitosis were lower than controls and values for third mitosis were higher than controls. Gbanding results showed that chromosome breaks were located on chromosomes 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 (Fucic et al. 1995).

It has been suggested that members of the *ras* gene family, including Ha-*ras*, Ki-*ras,* and N-*ras, are* responsible for the control of cell proliferation and differentiation (Froment et al. 1994). DNA adducts

can cause point mutations in these genes, and vinyl chloride exposure can cause the formation of DNA adducts, as discussed later in this section. The c-Ki-ras2 gene has been found in hepatic angiosarcomas of workers exposed to high levels of vinyl chloride; this specific gene was shown to be activated by a GC→AT transition at the second base of codon 13 (Marion et al. 1991).

Analysis of serum samples taken from workers at French vinyl chloride polymerization plants showed that 4 out of 5 of those who developed angiosarcoma of the liver, 8 out of 9 who developed benign angiomatous lesions, and 22 out of 45 who had no evidence of liver lesions were positive for the presence of a mutant protein corresponding with the mutation of the c-Ki-*ras* gene (DeVivo et al. 1994). This mutant protein was not found in the serum of any of the unexposed controls. A linear relationship was found between the frequency of the mutant protein in serum and the number of years of exposure, which might provide evidence for the linearity of carcinogenicity risk in humans (DeVivo et al. 1994).

The p53 tumor suppressor gene is mutated in a variety of human cancers (Trivers et al. 1995). A study was performed to examine the p53 tumor suppressor genes and the murine double mm-2 (MDM2) proto-oncogenes from tumors of five vinyl chloride workers, four with angiosarcoma of the liver and one with hepatocellular carcinoma (Hollstein et al. 1994). The p53 tumor suppressor gene was being tested for mutation, while the MDM2 proto-oncogene was being tested for amplification. No amplification of the MDM2 gene was detected; however, adenosine-to-thymidine m&sense mutations were found in the p53 gene in two of the angiosarcoma cases. Data from a study of angiosarcoma of the liver cases in which there was no vinyl chloride exposure indicated that p53 mutations were uncommon, providing support for the specificity of p53 mutations with vinyl chloride exposure in cases of angiosarcoma of the liver (Soini et al. 1995).

Animal studies of rats and mice exposed via inhalation to vinyl chloride have concentrated on identifying direct effects on the DNA. Increased alkylation of liver DNA and increased cell proliferation were reported by Eaib et al. (1989). Both young and old rats were exposed to 600 ppm for 6 hours. The older male rats were sacrificed, and the young rats of both sexes and the adult females received a second 6-hour exposure following a 15-hour interval. The 30 young rats were apparently more susceptible to the effects of vinyl chloride, but only 3 male adults and 2 female adults were used for comparison.

When rat liver tumors induced by exposure to 500 ppm vinyl chloride were examined for mutations at codons 12, 13, and 61 of the Ha-*ras,* Ki-*ras*, and N-*ras* genes, an activating AT→TA transversion of base 2 of codon 61 of the Ha-ras was detected in the two hepatocellular carcinomas examined (Froment et al. 1994). Since this mutation was not detected in any of the five liver angiosarcomas examined in this study, the study authors suggested that there might be cell-specific factors that affect the RAS gene. Other mutations in codons 13 and 36 of the N-ras A gene were found in two out of five of the liver angiosarcomas examined (Froment et al. 1994). In contrast to the study by Marion et al. (1991) that was discussed previously, which showed the activation of the Ki-ras gene in hepatic angiosarcomas of vinyl chloride workers, the study by Froment et al. (1994) showed few relevant ras mutations in rat hepatic angiosarcomas. This suggests differing mechanisms of carcinogenesis in humans and rats.

The role of chloroethylene oxide, a metabolite of vinyl chloride, was described by Gwinner et al. (1983). Rats exposed to 2,000 ppm vinyl chloride for 8 hours per day, 5 days per week, for 3 weeks beginning at 7 days of age demonstrated hepatocellular ATPase-deficient foci and alkylation of liver DNA. Rats exposed to either 2,2'-dichloro-diethylether(bis(chloroethyl)ether) or to chloroethanol did not form these foci, which are considered to be preneoplastic; these compounds do not metabolize to chloroethylene oxide, but rather to the aldehyde, suggesting that the aldehyde is not a mutagen *in vivo*.

The types of adducts of vinyl chloride seen after in vivo exposure may depend on the length of exposure, the sensitivity of the method used, and on the animal species. The vinyl chloride-derived nucleoside, N-2,3-ethenoguanosine, has been identified in the liver of vinyl chloride-exposed rats. This nucleoside, when incorporated into DNA, has been shown to be an efficient mutagen that causes base-pair (i.e., purine-to-purine or pyrimidine-to-pyrimidine exchange) transitions during transcription (Singer et al. 1987). The identification of the etheno nucleosides has been reported to occur following inhalation exposure to vinyl chloride in rats (Bolt et al. 1986; Ciroussel et al. 1990; Eberle et al. 1989; Fedtke et al. 1990; Swenberg et al. 1992). Immature rats exposed in *vivo* formed six times more of this nucleoside, which correlated with the age-related sensitivity to carcinogenesis in these animals (Ciroussel et al. 1990). This age-related sensitivity to DNA adduct formation was also noted in an inhalation study of lactating rats and their lo-day-old pups exposed 4 hours per day, for 5 days to 600 ppm of vinyl chloride (Fedtke et al. 1990). Concentrations of two adducts found in the liver of the pups were fourfold higher than those found in the liver of the dams

Effects of vinyl chloride on DNA are not restricted to the rat. Induction of single-strand breaks in liver DNA of mice after inhalation of vinyl chloride was reported by Walles et al. (1988).

Vinyl chloride has not been shown to be positive for dominant lethal effects in rats exposed to up to 30,000 ppm for 6 hours per day, for 5 days (Anderson et al. 1976; Purchase et al. 1975; Short et al. 1977). The studies showed no evidence of pre- or post-implantation loss among the untreated females mated to the exposed males. These results indicate that no germinal mutations were caused by these acute exposures. Table 2-5 lists the key *in vivo* studies of the genotoxicity of vinyl chloride.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

The most compelling evidence for the carcinogenic potential of vinyl chloride in humans comes from the cluster of reports of greater than expected incidences of angiosarcoma of the liver in workers occupationally exposed to vinyl chloride (Byren et al 1976; Creech and Johnson 1974; Fox and Collier 1977; Infante et al. 1976b; Jones et al. 1988; Laplanche et al. 1992; Monson et al. 1975; Pirastu et al. 1990; Rinsky et al. 1988; Simonato et al 1991; Teta et al. 1990; Theriault and Allard 1981; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989). Angiosarcoma of the liver is considered to be a very rare type of cancer (25-30 cases per year in the United States) (Heath et al. 1975). However, approximately 30 years after the introduction of vinyl chloride for use in the industrial production of PVC, it became apparent that workers exposed to high levels of vinyl chloride had an unusually high incidence of this type of tumor. Investigators identified an increased likelihood of developing hepatic angiosarcoma among those exposed to the highest levels of vinyl chloride and those exposed to vinyl chloride for the longest duration (Fox and Collier 1977; Infante et al. 1976b; Jones et al. 1988; Rinsky et al. 1988; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989) Based on this information, vinyl chloride is considered to be a carcinogen in humans (EPA 1994c; IARC 1987).

Histopathological examination of liver tissue from humans with hepatic angiosarcoma has led to the hypothesis that angiosarcoma develops as a result of hyperplastic changes in sinusoidal cells. Areas of transition to angiosarcoma contained greatly increased numbers of sinusoidal cells with greatly expanded sinusoidal spaces. Also, hepatic cells were replaced by fibrous tissue forming trabeculae.

These areas also showed infiltration of angiosarcoma cells. In fully developed angiosarcoma, multiple areas with nodules of angiosarcoma cells were noted, the centers of which exhibited hemorrhagic necrosis (Popper et al. 1981).

Other cancers that have shown a statistically significant increase in mortality among vinyl chloride workers, in at least some studies, include cancer of the brain and central nervous system, the lung and respiratory tract, and the lymphatic/hematopoietic system. With regard to cancer of the brain and central nervous system, Cooper (1981), Waxweiler et al. (1976), and Wong et al. (1991) reported statistically significant increases; Monson et al. (1975) reported an increase in central nervous system cancer mortality in a proportional mortality study; Byren et al. (1976), Simonato et al. (1991), and Tabershaw and Gaffey (1974) reported increases that were not statistically significant; and Fox and Collier (1977), Jones et al. (1988), Thomas et al. (1987), and Wu et al. (1989) found no increase in cancer of the central nervous system among workers occupationally exposed to vinyl chloride. It should be noted that the Cooper (1981), Tabershaw and Gaffey (1974), and Wong et al. (1991) studies were all based on the same cohort from a Chemical Manufacturers Association (CMA) study (Wong and Whorton 1993). Workers in the studies by Waxweiler et al. (1976) and Wu et al. (1989) were also employed at the same plants used for the CMA study (Wang and Whorton 1993). At least one analysis of epidemiological studies exposed certain weaknesses in the data that support a causal link between vinyl chloride and brain cancer (Doll 1988).

A significant increase in cancer of the respiratory tract was reported by Belli et al. (1987), Infante et al. (1976b), and Waxweiler et al. (1976) and also by Monson et al. (1975) in a proportional mortality study. However, studies by Cooper (1981), Fox and Collier (1977), Jones et al. (1988), Simonato et al. (1991), Wong et al. (1991), and Wu et al. (1989) did not find a significant increase. Although smoking history was not considered in the studies reporting a statistically significant increase in respiratory cancer, Waxweiler et al. (1976) noted that the types of respiratory tract cancer most frequently recorded were large-cell undifferentiated carcinoma or adenocarcinoma, which are two lung cancer types not usually associated with smoking.

A statistically significant increase in cancers of the lymphatic/hematopoietic system was reported by Rinsky et al. (1988), Smulevich et al. (1988), and Weber et al. (1981). Monson et al. (1975) also reported an increase in their proportional mortality study. However, no statistically significant increase

in these types of cancer was reported by Infante et al. (1976b), Jones et al. (1988), or Wong et al. (1991).

An increased incidence of malignant melanoma among vinyl chloride workers has been reported (Heldaas et al. 1984, 1987), but the significance of this finding has been disputed (Ten Berge 1987).

Few studies directly address the incidence of cancer in women occupationally exposed to vinyl chloride. However, one study found that women employed in the production of vinyl chloride and PVC had a significantly greater chance of developing leukemia or lymphomas (Smulevich et al. 1988). Furthermore, the subgroup of women who were exposed to the highest levels of vinyl chloride had increased incidences of stomach cancer and the highest incidences of leukemia and lymphoma. No significant increase in any type of cancer was observed in exposed males in this report, irrespective of the level of exposure.

Studies in several species support the conclusion that vinyl chloride is carcinogenic. A large series of experiments was performed by Maltoni et al. (1981) using rats (Sprague-Dawley and Wistar), mice, and hamsters. All animals were chamber exposed; controls were chamber exposed to air only. The test material was >99.9% pure. A complete gross and histopathological examination of every animal was performed. However, extremely limited histopathological data were presented and cancer incidences were presented only in summary tables. Also, survival of control animals was poor in some of the experiments, suggesting that animal care was inadequate or that unthrifty animals were used. Furthermore, statistical analyses, where present, appear to be based on a compilation of data from several individual studies. In one group of studies, Maltoni et al. (1981) exposed Sprague-Dawley rats to vinyl chloride for 52 weeks at concentrations ranging from 1 to 30,000 ppm. Animals were examined at the time of their spontaneous death. Statistically significant increases were noted in the incidence of mammary gland carcinomas at concentrations as low as 5 ppm in females, Zymbal gland carcinomas at 10,000 ppm and above, nephroblastoma at concentrations as low as 100 ppm in males and 250 ppm in females, liver angiosarcoma at concentrations as low as 50 ppm in females and 200 ppm in males, neuroblastoma at 10,000 ppm in females, and forestomach papillomas and acanthoma at 30,000 ppm. Other findings (though not statistically significant) that were considered important, based on historical data from their laboratory that indicated the rarity of certain tumors, include angiosarcoma and Zymbal gland carcinoma at 10 and 25 ppm and nephroblastoma at 25 ppm. Exposure of Swiss mice to 50 ppm vinyl chloride for 4 hours per day, 5 days per week for 30 weeks

also appeared to increase the incidence of liver angiosarcoma and angioma (Maltoni et al. 1981). Maltoni et al. (1981) also reported that decreasing the duration of exposure decreased the incidence of vinyl chloride-related tumors (nephroblastomas, liver angiosarcomas, Zymbal gland carcinomas, and to some extent, neuroblastomas), but statistics were not presented to support this conclusion.

Some variation in the target organs that developed tumors was observed when different species were exposed to vinyl chloride (Maltoni et al. 1981). Whereas angiosarcomas of the liver were reported to occur in rats, mice, and hamsters, mammary gland carcinomas were found only in rats and mice; Zymbal gland carcinomas, neuroblastomas, and nephroblastomas were found only in rats; lung tumors were found only in mice; and melanomas, acoustical duct epithelial tumors, and leukemias were found only in hamsters.

Other inhalation experiments support the carcinogenicity of vinyl chloride. Rats and mice exposed to 0, 50, 250, or 1,000 ppm for 6 hours per day, 5 days per week, for 6 months (Hong et al. 1981) or up to 12 months (Lee et al. 1977a, 1978) had a significantly increased incidence of hemangiosarcoma of the liver at 2250 ppm. Increases in bronchiole-alveolar adenoma of the lung and mammary gland tumors (adenocarcinomas, squamous and anaplastic cell carcinomas) were also observed in mice at 250 ppm, although it is unclear whether the increases in these tumor types are statistically significant (Lee et al. 1977a, 1978). Male rats exposed to concentrations as low as 100 ppm for 6 hours per day, 6 days per week, for 12 months had significantly increased incidence of cancer, including angiosarcoma of the liver and lung, when sacrificed at 18 months (Bi et al. 1985). Rats exposed to 30,000 ppm vinyl chloride 4 hours per day, 5 days per week, for 12 months had an increased incidence of epidermoid carcinoma of the skin, adenocarcinoma of the lungs, and osteochondroma in the bones (Viola et al. 1971), and rats exposed to 5,000 ppm for 52 weeks had primary tumors in the brain, lung, Zymbal gland, and nasal cavity (Feron and Kroes 1979). However, these studies (Feron and Kroes 1979; Viola et al. 1971) are limited by the absence of statistical analysis of the data. A concentration-dependent increase in tumor formation (alveologenic adenomas of the lung, angiosarcomas of the liver, and adenosquamous carcinoma of the mammary gland) was observed in mice exposed to 0, 50, 200, or 2,500 ppm vinyl chloride in a study performed for the Manufacturing Chemists Association (Keplinger et al. 1975). However, no statistics were presented to support these conclusions. Furthermore, an audit of data performed for the Manufacturing Chemists Association (EPL 1979) indicated that mishandling of the tissues precluded making statements regarding the relationship of tumors other than angiosarcoma of the liver to vinyl chloride exposure. Female mice

exposed to 50 ppm vinyl chloride showed increased incidence of hemangiosarcoma of the subcutis and peritoneum as well as tumors of the lung and mammary gland (Drew et al. 1983), i.e., hemangiosarcoma of the skin, spleen, or liver and mammary gland carcinomas.

In a preliminary study with a limited number of animals, alveogenic lung tumors developed in 26 of 27 mice exposed to 2,500 or 6,000 ppm for 5-6 months (Suzuki 1978). A concentration-related increase in the incidence of alveogenic tumors was observed in a study in which a greater number of mice were exposed to O-600 ppm for 4 weeks and then observed for up to 40 weeks postexposure (Suzuki 1983). The lowest concentration at which multiple foci tumors were observed was 100 ppm (Suzuki 1983.) A significant increase in the incidence of pulmonary adenomas was reported in mice exposed to 50 ppm 6 hours per day, 5 days per week for 6 months (Adkins et al. 1986). An increase in bronchio-alveolar adenoma was observed in a lifespan study in mice that were exposed to 50 ppm for 100 l-hour exposures, 500 ppm for 10 l-hour exposures, or 5,000 ppm for a single l-hour exposure (Hehir et al. 1981). The statistical significance of these observations was not presented.

Some data suggest that exposure of animals early in their lives may increase the likelihood of developing tumors or affect the type of tumor that develops. When hamsters, mice, and rats were exposed to vinyl chloride for periods of 6-24 months starting at various times after weaning, the incidence of tumors such as hemangiosarcoma of the liver, skin, and spleen, and angiosarcoma of the stomach was greater when animals were exposed for 12 months immediately after weaning than if animals were held for 12 months and then exposed for the next 12 months (Drew et al. 1983). Mammary gland carcinoma was also significantly increased when 2- or g-month-old hamsters, but not 14- or 20-month-old hamsters, were exposed to 200 ppm vinyl chloride for 6 months (Drew et al. 1983). Fibroadenoma of the mammary gland was also increased in female rats exposed to 100 ppm of vinyl chloride for 6 hours per day, 5 days per week, over 6-24 months (Drew et al. 1983). Also, when pregnant rats were exposed to 6,000 ppm vinyl chloride from gestation day 12 through 18, the incidence of mammary gland carcinomas, Zymbal gland carcinomas, and forestomach epithelial tumors was reported to be greater in transplacentally exposed animals than in maternal animals (Maltoni et al. 1981). At 10,000 ppm in this study, nephroblastomas were increased in transplacentally exposed animals compared to maternal animals (Maltoni et al. 1981). No control group was used, however, and no statistics were presented to support the conclusions. Maltoni and Cotti (1988) also exposed pregnant rats to 2,500 ppm vinyl chloride starting on gestation day 12 and continued to expose both maternal animals and offspring for a total of 76 weeks. Hepatocarcinoma, hepatic angiosarcoma, and

neuroblastoma were increased in treated animals compared to controls. The incidence of hepatocarcinoma was reported to be much higher in offspring than in maternal animals. In contrast, the incidence of neuroblastomas was similar between offspring and parents, and hepatic angiosarcomas had only a slightly higher incidence and slightly shorter latency in offspring than parents. However, no statistics were presented to support these conclusions.

Many of the tumors that were observed in the Drew et al. (1983) and Maltoni et al. (1981) studies were also observed in a study performed by Froment et al. (1994). In this study, Sprague-Dawley pups were exposed to 500 ppm vinyl chloride 8 hours/day, 6 days/week, on postpartum days 3-28. After weaning, 22 animals/sex were exposed for an additional 2 weeks, for a total exposure duration of 33 days. All livers from exposed animals that appeared normal at gross examination were found to contain multiple nodular hyperplastic foci of hepatocytes. Liver tumors that were found in exposed animals included angiosarcomas, hepatocellar carcinomas, and benign cholangiomas. Other tumors found included pulmonary angiosarcoma (probably metastatic), nephroblastoma, abdominal angiomyoma, leukemia, Zymbal gland carcinoma, pituitary adenoma, mammary carcinoma, and mammary fibroma. Tumor incidence was not reported in control animals, but it was assumed to be negative. Only one concentration (500 ppm) of vinyl chloride was used because the purpose of the study was to examine the genotoxicity of vinyl chloride in liver tumors produced by exposure.

The c-Ki-rus2 gene has been found in hepatic angiosarcomas of workers exposed to high levels of vinyl chloride (Marion et al. 1991). This gene, activated by a GC→AT transition at base 2 of codon 13, is a member of the rus gene family (Marion et al. I991). It has been suggested that this gene family is in control of cell proliferation and differentiation and that adducts may be responsible for point mutations in these genes (Froment et al. 1994). Further evidence for the genotoxic effects of vinyl chloride comes from the formation of DNA adducts after vinyl chloride exposure *in vivo. The* vinyl chloridederived nucleoside, N-2,3-ethenoguanosine, has been identified in the liver of vinyl chloride+zxposed rats. This nucleoside, when incorporated into DNA, has been shown to be an efficient mutagen that causes base-pair (i.e., purine-to-purine or pyrimidine-to-pyrimidine exchange) transitions during transcription (Singer et al. 1987). The identification of the etheno nucleosides has been reported to occur following inhalation exposure to vinyl chloride in rats (Bolt et al. 1986; Ciroussel et al. 1990; Eberle et al. 1989; Fedtke et al. 1990; Swenberg et al. 1992). Immature rats exposed *in vivo* formed six times more of this nucleoside, which correlated with the age-related sensitivity to carcinogenesis in these animals (Ciroussel et al. 1990). This age-related sensitivity to

DNA adduct formation was also noted in an inhalation study of lactating rats and their lo-day-old pups exposed 4 hours per day, for 5 days to 600 ppm of vinyl chloride (Fedtke et al. 1990). Concentrations of two adducts found in liver of pups were fourfold higher than those found in liver of dams. Further information on formation of DNA adducts can be found in Section 2.2.1.7.

In general, the available evidence from inhalation studies in animals supports the finding in humans; that vinyl chloride is a carcinogen by this route of exposure. The lowest doses tested that produced a tumorigenic response CEL for each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

2.2.2 Oral Exposure

All dosages of vinyl chloride administered in the diet are reported as mg/kg(body weight)/day unless otherwise specified.

2.2.2.1 Death

No studies were located regarding lethal effects in humans following oral exposure to vinyl chloride.

No studies were located regarding acute or intermediate lethal effects of vinyl chloride in animals. However, decreased longevity has been observed in rats as a result of chronic ingestion of vinyl chloride. Significant increases in mortality were observed by Feron et al. (1981) when Wistar rats were allowed to consume vinyl chloride doses as low as 5.6 mg/kg/day in the diet for 4 hours per day over a 2-year period. Also, the effects of consumption of vinyl chloride during a lifespan study in Wistar rats lasting almost 3 years (149 weeks) were examined by Til et al. (1983, 1991). These authors found decreased survival at a vinyl chloride dosage of 1.7 mg/kg/day. In both of these studies, vinyl chloride was administered by incorporating PVC resin that was high in vinyl chloride content into the diet. In the Til et al. (1991) study, the diets of the control animals contained 1% PVC powder that did not contain residual vinyl chloride. Vaporization of vinyl chloride from the diets was limited by presenting feed containing the vinyl chloride to the rats for only a 4-hour period.

All reliable LOAEL values for death in rats following chronic exposure are recorded in Table 2-2 and plotted in Figure 2-2.

TABLE 2-2. Levels of Significant Exposure to Vinyl Chloride - Oral

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency/ (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		Serious (mg/kg/day)		Reference
	CHRONIC EXPOSURE								
	Death								
1	Rat (Wistar)	2 yr 5d/wk 4hr/d (F)					5.6	(100% died)	Feron et al. 1981
2	Rat (Wistar)	149 wk 4hr/d (F)					1.7	(increased mortality)	Til et al. 1983, 1991
	Systemic								
3	Rat (Wistar)	2 yr 5d/wk 4hr/d (F)	Hemato	5.6	17	(decreased clotting time)			Feron et al. 1981
			Hepatic		1.8	(cellular alteration)	5.6 F 17 M	(extensive necrosis) (extensive necrosis)	
4	Rat (Wistar)	2 yr 1x/d (GO)	Derm		30	(increased skin thickness, collagen)			Knight and Gibbons 1987

TABLE 2-2. Levels of Significant Exposure to Vinyl Chloride - Oral (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency/ (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
5	Rat (Wistar)	149 wk 4hr/d (F)	Hemato	1.7			Til et al. 1983, 1991
			Hepatic		0.018[b] F (basophilic foci of cellular alteration) 1.7 M (clear or basophilic foci of cellular alteration)	1.7 F (hepatic cysts)	
			Bd Wt	1.7			
	Cancer						
6	Rat (Wistar)	2 yr 5d/wk 4hr/d (F), (GO)				1.8 F (CEL: neoplastic nodules of liver) 5.6 M (CEL: angiosarcoma of lung; neoplastic nodules of liver, hepatic angiosarcoma)	Feron et al. 1981
7	Rat (Sprague-Dawley)	52 wk 5x/wk (GO)				0.3 (CEL: liver angiosarcoma, hepatoma)	Maltoni et al. 1981
8	Rat (Sprague-Dawley)	52 wk 5x/wk (GO)				16.65 F (CEL: liver angiosarcoma) 50 M (CEL: liver angiosarcoma)	Maltoni et al. 1981

TABLE 2-2. Levels of Significant Exposure to Vinyl Chloride - Oral (continued)

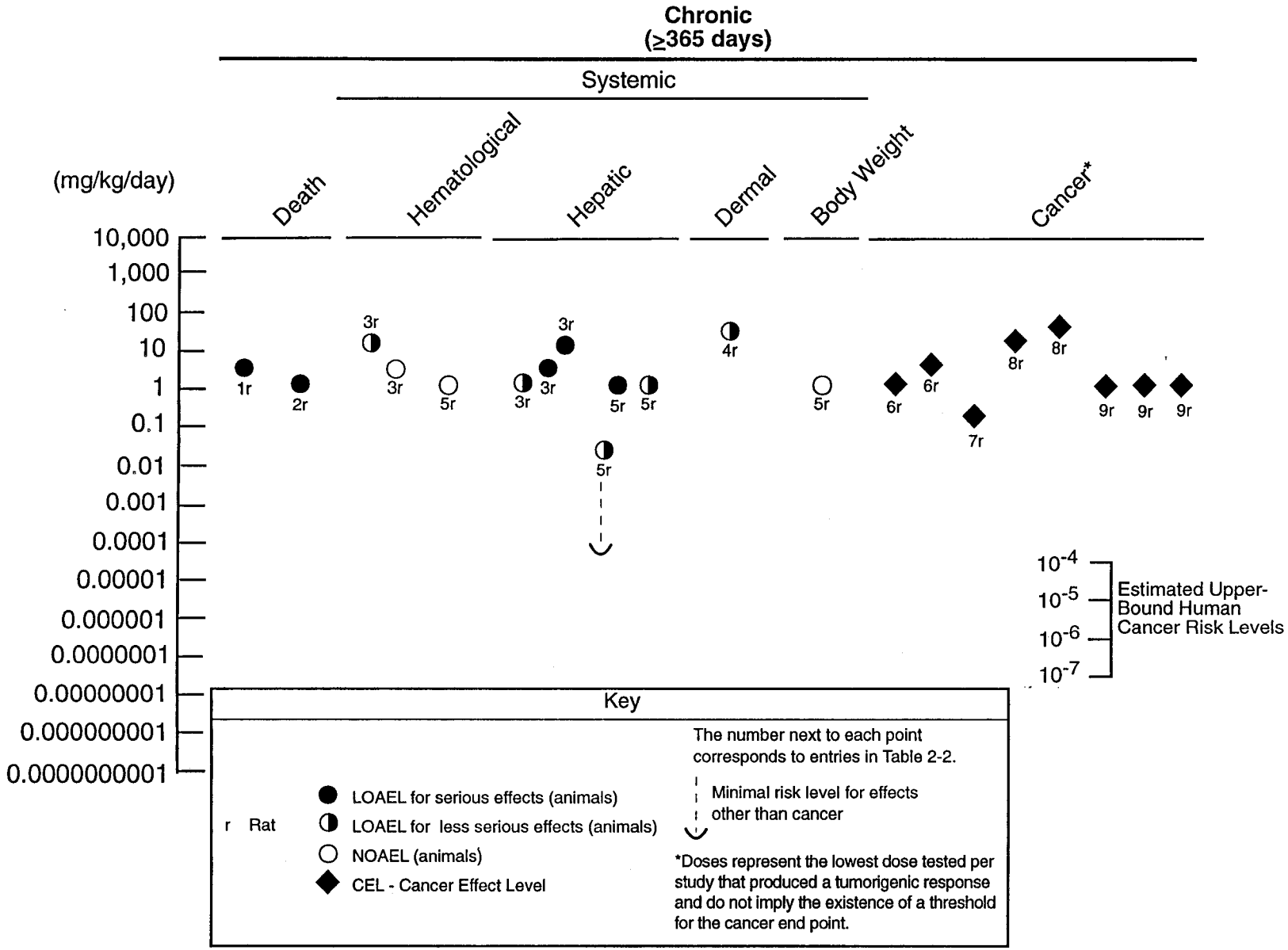
Key to figure[a]	Species/ (strain)	Exposure duration/ frequency/ (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
9	Rat (Wistar)	149 wk 4hr/d (F)				1.7 B (CEL: hepatic angiosarcoma) 1.7 M (CEL: hepatocellular carcinoma) 1.7 F (CEL: neoplastic nodules of liver)	Til et al. 1983, 1991

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive a chronic oral Minimal Risk Level (MRL) of 0.00002 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

B = both; Bd Wt = body weight; CEL = Cancer Effect Level; d = day(s); Derm = dermal; F = female; (F) = feed; (GO) = gavage-oil; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; wk = week(s); x = time(s); yr = year(s)

Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Oral



2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for hematological, hepatic, dermal, and body weight effects in rats following chronic oral exposure are recorded in Table 2-2 and plotted in Figure 2-2.

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, renal, or ocular effects in humans or animals following oral exposure to vinyl chloride.

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to vinyl chloride.

Rats fed 17 mg/kg/day for 2 years showed decreased clotting time of the blood, which was not observed at 5.6 mg/kg/day (Feron et al. 1981). No changes in thrombocyte count or prothrombin times were noted in Wistar rats fed diets containing high concentrations of vinyl chloride in PVC resin (1.7 mg/kg/day) for 149 weeks (Til et al. 1983, 1991).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to vinyl chloride.

Chronic exposure of rats to vinyl chloride in their feed for 149 weeks caused an increase in the incidence of basophilic foci of cellular alteration at 0.018 mg/kg/day (Til et al. 1983, 1991). This dose was used as the basis for a chronic oral MRL of 0.00002 mg/kg/day. Chronic oral exposure of rats fed vinyl chloride daily during a d-hour period for 2 years also resulted in areas of hepatocellular alteration at concentrations as low as 1.8 mg/kg/day (Feron et al. 1981). In this study, areas of necrosis were observed in the liver of female rats fed 5.6 mg/kg/day and male rats fed 17 mg/kg/day (Feron et al. 1981). Increased incidence of hepatic cysts were found in female rats fed 1.7 mg/kg/day and clear or basophilic areas of cellular alteration were found in male rats fed 1.7 mg/kg/day in the Til et al. (1983, 1991) studies.

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to vinyl chloride.

Daily administration of 30 mg/kg of vinyl chloride to rats by gavage for 2 years caused increased thickness, moisture content, and collagen content of the skin. Newly synthesized intermolecular and intramolecular collagen crosslinks were also significantly increased (Knight and Gibbons 1987).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to vinyl chloride.

No changes in body weight were noted in Wistar rats fed 1.7 mg/kg/day vinyl chloride mixed with PVC powder in the diet for 149 weeks (Til et al. 1983, 1991).

No studies were located regarding the following health effects in humans or animals after oral exposure to vinyl chloride:

2.2.2.3 Immunological and Lymphoreticular Effects

2.2.2.4 Neurological Effects

2.2.2.5 Reproductive Effects

2.2.2.6 Developmental Effects

2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to vinyl chloride.

Four studies were located that examined the carcinogenic potential of vinyl chloride in animals when administered by the oral route. In two of these studies, conducted for 149 weeks, vinyl chloride was added to the diet by incorporating PVC powder containing a high level of the monomer (Feron et al. 1981; Til et al. 1983, 1991). To limit volatilization of vinyl chloride from the diet, the rats were

allowed access to the diet for only 4 hours per day. The actual intake of vinyl chloride in these reports was calculated by taking into consideration both the food consumption and the rate of vinyl chloride evaporation. Statistically significant increases in hepatic angiosarcoma of the liver were observed in the 2-year study by Feron et al. (198 1) at 5.6 mg/kg/day in males and 17 mg/kg/day in females. In the same study, statistically significant increases in neoplastic nodules of the liver were also observed at a concentration of 5.6 mg/kg/day in males but as low as 1.8 mg/kg/day in females (Feron et al. 1981). Also, in the 149-week study by Til et al. (1983, 1991), statistically significant increases in hepatocellular carcinoma were observed in males at 1.7 mg/kg/day and hepatic neoplastic nodules in females at 1.7 mg/kg/day. A few animals exposed to 1.7 mg/kg/day in this study developed hepatic angiosarcoma. An increased incidence of Zymbal gland tumors was also observed in the study by Feron et al. (1981). Although the increase was not statistically significant, the tumors were considered to be treatment related based on the historical rarity of this type of tumor.

Two studies were located in which vinyl chloride was administered to Sprague-Dawley rats by gavage for 52 weeks. In one of these studies, a statistically significant increase in the incidence of hepatic angiosarcomas was observed at doses as low as 16.65 mg/kglday in females and 50 mg/kg/day in males. Zymbal gland tumors at 16.65 and 50 mg/kg/day, even though not statistically significant, were considered to be treatment related because of the rarity of this type of tumor (Maltoni et al. 1981). Lower doses of vinyl chloride were also tested in a similar study in which hepatic angiosarcomas were observed at doses as low as 0.3 mg/kg/day and Zymbal gland tumors at 1 mg/kg/day. Although neither of these findings reached statistical significance, the tumors were considered to be treatment related because of the historically rare observation of these tumor types in the colony (Maltoni et al. 1981).

Based on the evidence of carcinogenicity in animals after oral exposure, it would be prudent to consider the potential for carcinogenic effects in humans by this route as well.

The lowest doses tested that produced a tumorigenic response (CEL) in rats chronically exposed to vinyl chloride by the oral route are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

Dermal exposure to vinyl chloride may occur by skin contact with either gaseous or liquid vinyl chloride. Negligible amounts of gaseous vinyl chloride are absorbed through the skin (see also Section 2.3.1.3 regarding absorption by the dermal route). However, dermal exposure can also occur by direct contact of gaseous vinyl chloride with the eyes. Only studies that specifically relate to dermal contact of liquid vinyl chloride or ocular effects occurring with inhalation exposure to gaseous vinyl chloride are discussed below.

2.2.3.1 Death

No studies were located regarding lethal effects in humans or animals after dermal exposure to vinyl chloride.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to vinyl chloride.

Dermal Effects. Vinyl chloride exists as a liquid when stored under pressure. However, when it is released from pressurized containers, it rapidly vaporizes into gas. Thus, the dermal effects observed after exposure to vinyl chloride are not unique to vinyl chloride but can be expected as a result of a rapidly evaporating liquid on the skin The effects are due to tissue freezing rather than direct toxicity of vinyl chloride. A man who had liquid vinyl chloride sprayed on his hands developed second degree burns. At first, the man reported that his hands felt numb. Within a short period, the hands had developed marked erythema and edema (Harris 1953).

No studies were located regarding dermal effects in animals after dermal exposure to vinyl chloride.

Ocular Effects. Local bums on the conjunctiva and cornea were observed in a man who died after exposure to an unknown quantity of vinyl chloride vapor escaping from an open valve (Danziger 1960).

No ocular effects were noted in guinea pigs exposed for 30 minutes to up to 400,000 ppm vinyl chloride in inhalation chambers (Mastromatteo et al. 1960).

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals following dermal exposure to vinyl chloride.

2.2.3.4 Neurological Effects

A man who had liquid vinyl chloride sprayed on his hands initially reported that his hands felt numb (Harris 1953).

No studies were located regarding neurological effects in animals after dermal exposure to vinyl chloride.

No studies were located regarding the following health effects in humans or animals after dermal exposure to vinyl chloride:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals following dermal exposure to vinyl chloride.

2.3 TOXICOKINETICS

Studies in humans and animals have shown that vinyl chloride is readily absorbed through the lungs. Vinyl chloride is volatile and exposure occurs largely by inhalation. Men exposed to vinyl chloride for 6 hours were reported to have relatively constant retention after about 30 minutes of exposure indicating that saturation of the major metabolic pathway did not occur (Krajewski et al. 1980). Rats exposed to vinyl chloride by inhalation were found to have peak blood levels after 30 minutes of exposure to 7,000 ppm, which decreased rapidly after removal (Withey 1976). No studies were located that reported the absorption of vinyl chloride after oral exposure in humans. In animals, vinyl chloride has been found to be rapidly and almost completely absorbed from the gastrointestinal tract after oral exposure (Watanabe et al. 1976a; Withey 1976), with peak blood levels occurring lo-20 minutes after dosing (Withey 1976). No studies were located that reported the absorption of vinyl chloride in humans after dermal exposure. Based upon a single study in monkeys, dermal absorption of vinyl chloride vapor is not likely to be significant (Hefner et al. 1975a).

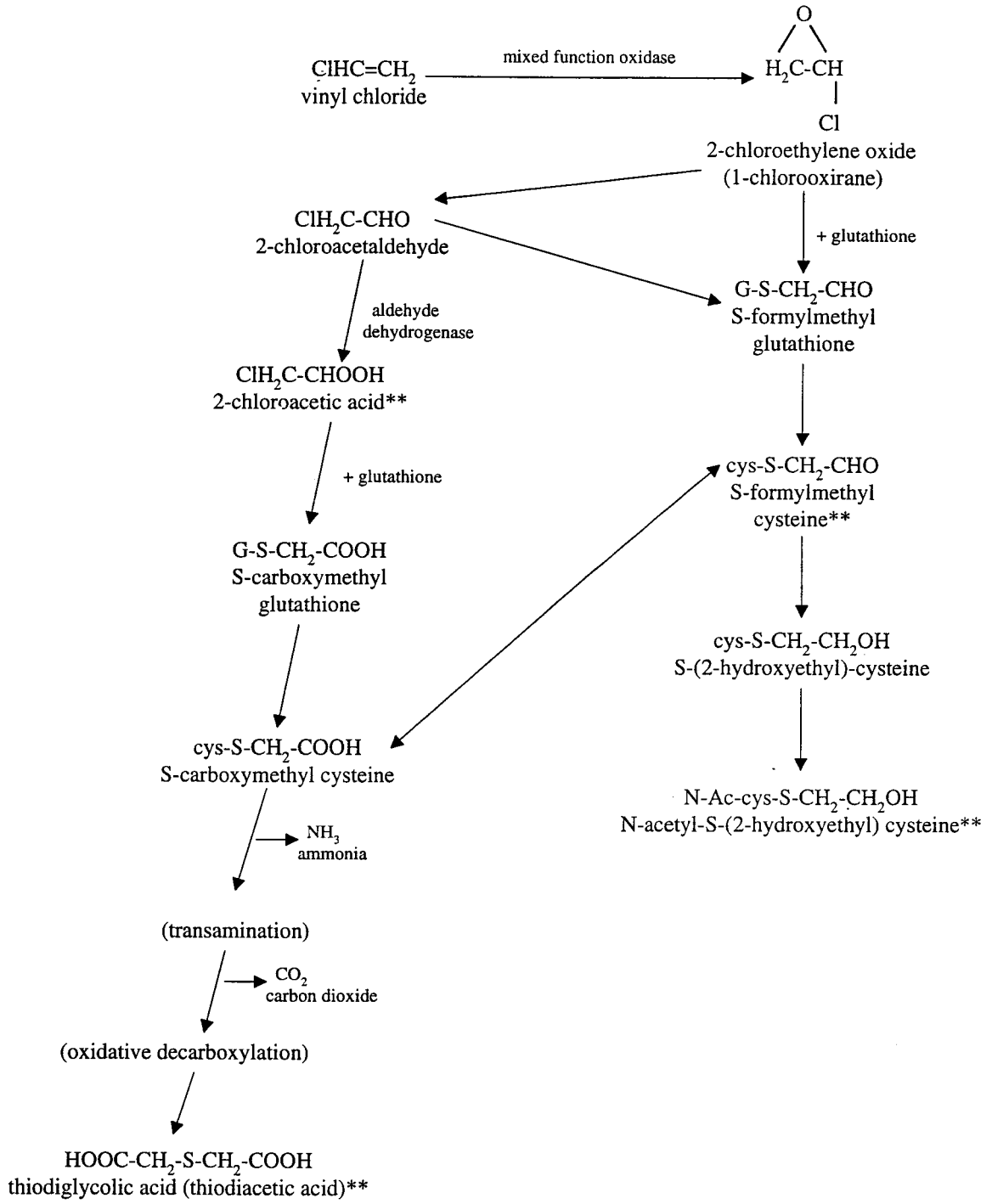
No studies were located that reported tissue distribution after inhalation, oral, or dermal exposure to vinyl chloride in humans or after dermal exposure in animals. Animal studies indicate that although vinyl chloride is largely eliminated via the lungs after inhalation, its distribution is rapid and widespread. However, its storage in the body is limited because of rapid metabolism and excretion. Metabolites of vinyl chloride have been found in the liver, kidney, spleen, skin, and brain as well as in other tissues, but the percentages in these tissues are relatively small (Bolt et al. 1976a; Buchter et al. 1977; Watanabe et al. 1976b). Vinyl chloride metabolites have not been shown to accumulate more in tissues after repeated exposure than after a single exposure (Watanabe et al. 1978a). Vinyl chloride has been found to cross the placenta after inhalation exposure (Ungvary et al. 1978). After a single oral dose of radiolabelled vinyl chloride in rats, radioactivity levels were much greater in the liver than in other tissues examined (skin, plasma, muscle, lung, fat, and carcass) (Watanabe et al. 1976a).

After inhalation exposure in humans, exhalation of unmetabolized vinyl chloride is not a major pathway of elimination at low concentrations (Krajewski et al. 1980). Animal studies have shown that exhalation of vinyl chloride as a major route of excretion, after inhalation exposure, is dependent upon the exposure concentration. In rats exposed to 10 ppm for 6 hours, 70% of radioactivity recovered consisted of metabolites excreted through the urine (Watanabe and Gehring 1976; Watanabe et al. 1976b). Saturation of metabolism occurred at 1,000 ppm. At 5,000 ppm, most vinyl chloride

appeared to be unmetabolized in expired air, and approximately 27% of recovered radioactivity had been excreted in urine (Watanabe et al. 1978a). The proportion of recovered radioactivity exhaled as carbon dioxide or excreted in feces changed very little with increased exposure concentrations. Pulmonary excretion of unaltered vinyl chloride followed first-order kinetics despite increases in exposure concentrations; urinary excretion of radioactivity was biphasic. No studies were located regarding excretion in humans after oral or dermal exposure to vinyl chloride. After dermal exposure in monkeys, most of the little vinyl chloride absorbed was excreted in exhaled air (Hefner et al. 1975a). Oral exposure of rats to vinyl chloride showed that metabolic saturation occurred at 20 mg/kg (Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a). At 100 mg/kg, both pulmonary excretion and urinary excretion of vinyl chloride or its metabolites, respectively, were biphasic, while pulmonary excretion of vinyl chloride was monophasic at less than 1 mg/kg (Watanabe et al. 1976a).

Vinyl chloride metabolism in humans is attributed to the cytochrome P-450 monooxygenases in the liver (Sabadie et al. 1980). Proposed pathways most currently accepted for the metabolism of vinyl chloride are shown in Figure 2-3. Metabolism has been shown to follow first-order kinetics in rats, with pathway saturation beginning to be noticeable at 100 ppm (Hefner et al. 1975b). Metabolism occurs via the oxidation of vinyl chloride by mixed function oxidases (MFO) to form an epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde. Intermediates are detoxified primarily via glutathione conjugation; conjugated products are excreted in urine as substituted cysteine derivatives. A rodent study using a pretreatment that inhibited cytochrome P-450 oxidation pathways indicated that metabolism through an MFO pathway that produced an epoxide intermediate was the primary route of metabolism (Bolt et al. 1977). Macromolecular binding has been attributed to the reactive intermediate 2-chloroethylene oxide, which binds to DNA and RNA (ribonucleic acid), and its reaction product, 2-chloroacetaldehyde, which binds to protein molecules (Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). No studies were located regarding vinyl chloride metabolism in humans after oral or dermal exposure or in animals after dermal exposure. Data obtained in rats after oral exposure to vinyl chloride indicate consistency with metabolic pathways proposed for inhalation exposure (Green and Hathway 1975, 1977; Watanabe and Gehring 1976; Watanabe et al. 1976a). Metabolic saturation appears to occur after a single gavage dose of between 1 and 100 mg/kg/day (Watanabe et al. 1976a).

Figure 2-3. Proposed Metabolic Pathways for Vinyl Chloride*



* Derived from Bolt et al. (1980); Cogliano and Parker (1992); Hefner et al. (1975b); Park et al. (1993); Plugge and Safe (1977)

** Excreted in urine

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Inhalation absorption of vinyl chloride is rapid in humans. Young adult male volunteers were exposec to vinyl chloride monomer concentrations of 2.9, 5.1, 11.7, or 23.5 ppm by gas mask for 6 hours (Krajewski et al. 1980). Retention was estimated by measuring the difference between inhaled and exhaled concentrations. An average retention of 42% was estimated. Although the results varied among the individuals tested, the percentage retained was independent of the concentration inhaled. Since retention did not change with increasing vinyl chloride concentrations, it appears that saturation of the major pathway of overall metabolism did not occur in this exposure regimen.

Animal data, while demonstrating that inhalation absorption of vinyl chloride occurs readily and rapidly, are not sufficient to quantitatively determine the proportion of an inhaled dose that is absorbed. Physiologically based pharmacokinetic (PBPK) models that have been developed to provide these estimates are discussed in Section 2.3.5. Peak blood levels occurred at 30 minutes in rats exposed (head only) to 7,000 ppm (Withey 1976). On removal from the vinyl chloride atmosphere, blood levels fell rapidly. After 2 hours, concentrations were barely detectable. Rats that had been pretreated with 6-nitro-1,2,3-benzothiadiazole to completely block the metabolism of vinyl chloride were placed in a closed chamber containing approximately 0.5 ppm radiolabelled (^{14}C) vinyl chloride (Bolt et al. 1977). Radioactivity in the chamber air declined only for the first 15 minutes of exposure, indicating that equilibrium between atmospheric and tissue levels of radioactivity had occurred, suggesting rapid uptake by the tissues of the rats. One might expect that people would be likely to equilibrate within 1 hour.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to vinyl chloride.

Several studies in rats indicate that vinyl chloride is rapidly and virtually completely absorbed from the gastrointestinal tract. Peak blood levels of vinyl chloride were observed within 10-20 minutes after dosing in rats administered single oral doses (44-92 mg/kg) of vinyl chloride in aqueous solution

(Withey 1976). Peak blood levels varied from 6 to greater than 40 μg/mL. Data from another study in which rats were administered single gavage doses of 0.05, 1, and 100 mg/kg vinyl chloride labelled with radioactive carbon (^{14}C-vinyl chloride) (in corn oil) suggested that almost complete absorption of vinyl chloride occurred (Watanabe et al. 1976a). The fraction of the administered dose recovered in the feces, roughly indicative of the proportion unabsorbed, ranged from 0.47% to 2.39%; total recovery ranged from 82.3% to 91.3%. Loss of radioactivity might be attributed either to experimental error or to incomplete sampling of the carcass. Fecal excretion was measured in rats fed 0, 1.8, 5.6, and 17.0 mg/kg/day of vinyl chloride monomer (from powdered PVC containing a high level of the monomer) (Feron et al. 1981). Fecal excretion accounted for 8%, lo%, and 17% of the vinyl chloride present in the low-, middle-, and high-dose groups, respectively. The investigators hypothesized that the vinyl chloride recovered from the feces was encapsulated by PVC and was not available to the rats for absorption, and that absorption of available vinyl chloride was virtually complete.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal exposure to vinyl chloride.

Animal data suggest that dermal absorption of vinyI chloride vapor is not likely to be significant. Dermal absorption was measured in two rhesus monkeys that received full body (except head) exposure to vinyl chloride gas. It was estimated that 0.031% and 0.023% of the total available vinyl chloride was absorbed at 800 and 7,000 ppm, respectively, after a 2-2.5hour exposure (Hefner et al. 1975a). The investigators concluded that, after short-term exposure to high concentrations, dermal absorption was far less significant than inhalation absorption.

2.3.2 Distribution

Representative vinyl chloride partition coefficients for humans, rats, mice, and hamsters can be found in Table 2-3. These partition coefficients were obtained for use in PBPK models. They were estimated using a vial equilibration technique (Air Force 1990b). Further details about how the values were obtained, including the number of experiments completed and whether the errors shown are standard deviations or standard errors, were not provided. In general, concentrations of vinyl chloride found in fat are higher than would be found in other tissues. Partition coefficients for vinyl chloride

TABLE 2-3. Vinyl Chloride Partition Coefficients

Partition coefficient

Species Strain Sex Blood/air Liver/air Muscle/air Fat/air

TABLE 2-3. Vinyl Chloride Partition Coefficients

Species	Strain	Sex	Partition coefficient			
			Blood/air	Liver/air	Muscle/air	Fat/air
Rat	CDBR[a]	M	1.8±0.22	3.0±0.41	2.2±0.70	14.6±0.92
		F	2.1±0.44	1.7±0.43	1.3±0.25	19.2±0.96
	F-344[a]	M	1.6±0.33	2.0±2.0	2.1±0.70	11.8±0.81
		F	1.6±0.11	2.1±0.17	2.4±0.46	21.1±1.3
	Wistar[a]	M	2.1±0.31	2.7±0.56	2.7±0.58	10.2±1.6
		F	1.6±0.07	1.5±0.28	1.6±0.22	22.3±0.54
	Sprague-Dawley[b]	M	2.4±0.5	-	-	-
Mouse	$B6C3F_1$[a]	M	2.8±0.22	-	-	-
		F	2.6±0.14	-	-	-
	CD-1[a]	M	2.3±0.07	-	-	-
		F	2.4±0.16	-	-	-
Hamster	Golden Syrian[a]	M	2.7±0.15	3.4±0.36	2.6±0.46	14.3±5.3
		F	2.2±0.47	1.3±0.28	2.0±0.28	21.1±2.0
Human[c]	NA	NR	1.16	-	-	-

[a]Air Force (1990b); values determined using vial equilibration method
[b]Barton et al. (1995)
[c]EPA (1987g)

- = no data; F = female; M = male; NA = not applicable; NR = not reported

range from 10 to 20 (fat/air) and from 1 to 3 (muscle/air, blood/air, and liver/air). In animal studies, females have shown greater partitioning to fat than males.

Tissue/blood partition coefficients in male Sprague-Dawley rats, measured using a vial equilibration method, have been reported as lo&3 for fat/blood, 0.4±0.2 for muscle/blood, 0.720.3 for liver/blood, and 0.7kO.4 for kidney/blood (Barton et al. 1995).

2.3.2.1 Inhalation Exposure

No studies were located regarding tissue distribution in humans after inhalation exposure to vinyl chloride.

Data from rat studies suggest that the distribution of inhaled vinyl chloride is rapid and widespread, but storage of vinyl chloride in the body is limited by rapid metabolism and excretion. In rats exposed to ^{14}C -vinyl chloride and pretreated with 6-nitro-1,2,3-benzothiadiazole to block metabolism of vinyl chloride by microsomal cytochrome P-450 oxidation pathways, the highest levels of radiolabel were located in the fat, with lesser amounts in the blood, liver, kidney, muscle, and spleen. When metabolism was not blocked, the highest levels of radiolabelled metabolites were located in the liver and kidney (Buchter et al. 1977). Immediately after a 5-hour exposure to ^{14}C-vinyl chloride at 50 ppm, tissue levels of ^{14}C -activity, expressed as the percentage incorporated per gram of tissue, were highest in the kidney (2.13%) and liver (1.86%), with lower levels in the spleen (0.73%) and brain (0.17%) (Bolt et al. 1976a). Radioactivity in tissue was measured in rats 72 hours after exposure to 10 or 1,000 ppm ^{14}C -vinyl chloride for 6 hours. In order of decreasing concentration for rats exposed to 10 ppm, ^{14}C -labeled compounds (expressed as percentage), present as nonvolatile metabolites, were measured in the liver (0.14), kidney (0.08), skin (0.07), lung (0.07), muscle (0.05), carcass (0.05), plasma (0.05), and fat (0.03). For rats exposed to 1,000 ppm, radiolabel (expressed as percentage) was measured in the liver (0.15), skin (0.12), kidney (0.06), carcass (0.05), lung (0.05), muscle (0.04), fat (not detected), and plasma (not detected) (Watanabe et al. 1976b). There was no difference in the routes or rate of excretion between repeated-dose versus single-dose exposure of rats to 5,000 ppm of ^{14}C -vinyl chloride (Watanabe et al. 1978a). The concentration of radiolabel detected in tissues 72 hours after exposure revealed no statistically significant difference between rats exposed once or repeatedly to vinyl chloride. Percentages of radioactivity after 72 hours measured in tissues are as

follows (for single and repeated doses, respectively): liver (0.12)(0.16), kidney (0.06)(0.07), skin (0.05)(0.08), carcass (0.03)(0.04), and fat (not detected)(not detected).

Placental transfer of vinyl chloride can occur rapidly in rats. Female rats exposed to approximately 0, 2,000, 7,000, or 13,000 ppm vinyl chloride for 2.5 hours on gestational day 18 showed high concentrations of vinyl chloride in maternal and fetal blood and amniotic fluid (Ungvary et al. 1978). Vinyl chloride concentrations in maternal blood were 19.02, 32.40, and 48.43 μg/mL, respectively, while fetal blood concentrations were 12.80, 22.67, and 30.52 μg/mL, respectively. Vinyl chloride concentrations in amniotic fluid were 0, 4.27, 4.93, and 13.50 μg/mL, at 2,000, 7,000, and 13,000 ppm vinyl chloride, respectively (Ungvary et al. 1978).

2.3.2.2 Oral Exposure

No studies were located regarding tissue distribution in humans after oral exposure to vinyl chloride.

The level of ^{14}C-nonvolatile metabolites was measured in tissues of rats 72 hours after single gavage doses (0.05-100 mg/kg) of ^{14}C-vinyl chloride in corn oil (Watanabe et al. 1976a). The highest levels of radioactivity for each dose level occurred in the liver. These levels were 2-5 times higher than in the other tissues examined (skin, plasma, muscle, lung, fat, and carcass).

2.3.2.3 Dermal Exposure

No studies were located regarding tissue distribution for humans or animals after dermal exposure to vinyl chloride.

2.3.3 Metabolism

2.3.3.1 Inhalation Exposure

Metabolism can be quantitatively estimated from gas uptake experiments in which, after initial absorption of vinyl chloride, continued absorption is largely attributed to metabolism. Krajewski et al. (1980) exposed young men to vinyl chloride monomer at concentrations of 2.9, 5.1, 11.7, and 23.5 ppm by gas mask for 6 hours. Retention was estimated by determining the difference between

the inhaled and exhaled concentrations. Individual variation was present; however, the percentage retained was found to be independent of the concentration inhaled. Since the retention did not change with increasing vinyl chloride concentrations, it appears that saturation of the major metabolic pathway did not occur in this exposure regimen.

Metabolism of vinyl chloride was attributed to the cytochrome P-450 monooxygenases in the S-9 fraction from surgically obtained human liver specimens. These preparations metabolized vinyl chloride to electrophiles that were mutagenic *to Salmonella* typhimurium TA1530 (Sabadie et al. 1980). Mutagenicity assays were performed by exposing the plates containing S. *typhimurium* and 150 μL human S-9 fraction to a gaseous mixture of 20% vinyl chloride in air for 4 hours. Vinyl chloride was removed after the exposure. The vinyl chloride concentration in the aqueous phase of the plates was $4x10^{-3}$ M. Incubation was continued for an additional 48 hours. When compared with the number of revertants per plate resulting from identically prepared S-9 fractions from female strain BD IV rats, human S-9 fractions induced mutations (and presumably metabolism to a reactive electrophile) to an average 84% of the extent mediated by rat S-9. However, a ninefold individual variation was observed.

The major metabolic pathway of vinyl chloride involves oxidation by mixed-function oxidases to form a highly reactive epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde (Guengerich et al. 1979, 1981; Gwinner et al. 1983; Laib 1982). These intermediates are detoxified mainly through conjugation with glutathione catalyzed by glutathione S-transferase. The conjugated products are excreted in urine as substituted cysteine derivatives and include thiodiglycolic acid, S-formyl-methylcysteine, and IV-acetyl-S-(2-hydroxyethyl)cysteine (Bolt et al. 1980; Hefner et al. 1975b). Urinary metabolites identified in rats exposed by inhalation include polar compounds at low exposure concentrations (Hefner et al. 1975b; Watanabe et al. 1976b) and 2-chloroacetic acid at high exposure concentrations (Hefner et al. 1975b).

Early work on the metabolism of vinyl chloride in animals indicated that metabolism is a dose dependent, saturable process. Rats were exposed to vinyl chloride in a closed chamber at concentrations of about 50-1,000 ppm for 52.5-356.3 minutes (Hefner et al. 1975b). Additional rats pretreated with ethanol (to inhibit alcohol dehydrogenase activity) or SKF 525-A (to inhibit microsomal oxidase activity) were similarly exposed. Metabolism, estimated by measuring the rate of disappearance of vinyl chloride from the closed system, followed first-order kinetics with a half-life of

86 minutes at less than 100 ppm. At greater than 220 ppm, metabolism was slowed to a half-life of 261 minutes, suggesting saturation of the pathway predominant at 100 ppm. Pretreatment with ethanol depressed the rate of metabolism by approximately 83% at less than 100 ppm but by approximately 47% at greater than 1,000 ppm. Pretreatment with SKF 525-A, however, had no effect at less than 100 ppm but depressed metabolism by 19% at greater than 1,000 ppm. The study authors postulated alternative pathways for vinyl chloride metabolism. They suggested that at low concentrations sequential oxidation to 2-chloroethanol, 2-chloroacetaldehyde, and 2-chloroacetic acid involving alcohol dehydrogenase (inhibited by pretreatment with ethanol) appeared to be the predominant pathway. Little 2-chloroacetic acid was formed, however, possibly because 2-chloroacetaldehyde conjugated rapidly with ubiquitous sulfhydryl groups. The authors further speculated that when the alcohol dehydrogenase pathway became saturated, 2-chloroethanol could be oxidized by catalase in the presence of hydrogen peroxide (H_2O_2) to a peroxide, which could undergo subsequent dehydration to form 2-chloroacetaldehyde. However, it appears that the only support for this proposed metabolism of vinyl chloride by alcohol dehydrogenase comes from studies demonstrating metabolic inhibition by alcohol. This is not recognized as a direct pathway for metabolism of vinyl chloride in modem PBPK modeling studies. It is possible that ethanol exerts its effects by inhibiting specific P-450 enzymes involved in the metabolic activation of vinyl chloride.

Isolated rat liver cells converted ^{14}C -vinyl chloride into nonvolatile metabolites (Hultmark et al. 1979). Using this *in vitro* technique, it was determined that metabolism was NADPH-dependent, located in the microsomal fraction of the liver, and probably involved an MFO. Pretreatment with 6-nitro-1,2,3-benzothiadiazole, an inhibitor of some microsomal cytochrome P-450 oxidation pathways, was sufficient to totally block the metabolism of vinyl chloride in rats exposed to 0.45 ppm in a closed system for 5 hours (Bolt et al. 1977). This observation suggests that metabolism of vinyl chloride proceeds primarily through an MFO pathway with likely production of an epoxide intermediate.

Inhalation exposure of high concentrations of vinyl chloride has also been associated with a reduction in the liver nonprotein sulfhydryl concentration in the rat (Barton et al. 1995). These results are consistent with conjugation of the metabolites of vinyl chloride with limited reserves of glutathione and/or cysteine (Bolt et al. 1976b; Hefner et al. 1975b; Jedrychowski et al. 1984; Watanabe et al. 1978b).

Saturation of metabolic pathways was observed in rats and monkeys that were exposed in a closed system to ^{14}C -vinyl chloride (Bolt et al. 1977; Buchter et al. 1980; Filser and Bolt 1979). In rats, metabolic saturation was determined to occur at approximately 250 ppm, and a metabolic rate (V_{max}) of 110 μmol/hour/kg was estimated (Bolt et al. 1977; Filser and Bolt 1979). Kinetic constants of 58 μmol/hour/kg for V_{max} and 1 μM for the K_m in male Sprague-Dawley rats have also been reported (Barton et al. 1995). In an experiment using rhesus monkeys, metabolic saturation occurred at 200 ppm, with a V_{max} of 50 μmol/hour/kg (Buchter et al. 1980). The V_{max} of 50 μmol/hour/kg that was estimated using rhesus monkeys was suggested as a closer approximation of metabolism in humans than the value of 110 μmol/hour/kg estimated for rats by Filser and Bolt (1979).

Several investigators have observed the binding of nonvolatile metabolites of ^{14}C -vinyl chloride to liver macromolecules *in vitro* and in rats exposed by inhalation (Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). In single-exposure experiments at different concentrations, the extent of macromolecular binding increased proportionately to the amount of vinyl chloride metabolized and disproportionately to the exposure concentration (Watanabe et al. 1978b). The extent of macromolecular binding was increased by repeated exposure to vinyl chloride (Watanabe et al. 1978a) and by pretreatment with phenobarbital (Guengerich and Watanabe 1979). Macromolecular binding has been attributed to the reactive intermediate 2-chloroethylene oxide, which has been shown to bind to DNA and RNA, and to its rearrangement product, 2-chloroacetaldehyde, which has been shown to bind to protein molecules (Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b).

2.3.3.2 Oral Exposure

No studies were located regarding metabolism in humans after oral exposure to vinyl chloride.

Urinary metabolites identified from rats ingesting ^{14}C-vinyl chloride are consistent with the metabolic pathways postulated for inhalation exposure, in particular with the formation of 2-chloroethylene oxide and 2-chloroacetaldehyde. Metabolites identified include N-acetyl-S-(2-hydroxyethyl)cysteine, 2-chloroacetic acid, and thiodiglycolic acid (Green and Hathway 1975, 1977; Watanabe and Gehring 1976; Watanabe et al. 1976a). Metabolic saturation appears to occur with a single gavage dose of between 1 and 100 mg/kg/day (Watanabe et al. 1976a).

2.3.3.3 Dermal Exposure

No studies were located regarding metabolism in humans or animals after dermal exposure to vinyl chloride.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Human data suggest that exhalation of unmetabolized vinyl chloride is not an important pathway of elimination at low exposure concentrations. The mean concentration in expired air for humans exposed for 6 hours to air containing 2.9-23.5 ppm ranged from 0.21 to 1.11 ppm, representing from 7.23% to 4.73% of the inhaled concentrations, respectively (Krajewski et al. 1980).

Animal studies indicate that the importance of exhalation of vinyl chloride as a major route of excretion varies with the exposure concentration. The mode of excretion of vinyl chloride and its metabolites following inhalation exposure of animals to different concentrations reflects the saturation of metabolic pathways. The cumulative excretion of radioactivity over a 72-hour postexposure period was measured in rats exposed to lO--1,000 ppm (Watanabe and Gehring 1976; Watanabe et al. 1976b) or 5,000 ppm (Watanabe et al. 1978a) ^{14}C -vinyl chloride for 6 hours. Radioactivity expired as carbon dioxide or vinyl chloride, excreted in the urine and feces, and retained in the carcass was expressed as a percentage of the total radioactivity recovered. The results suggest that metabolism was nearly complete at 10 ppm because less than 2% of the recovered radioactivity occurred as unchanged parent compound. The predominant route for excretion of radioactive metabolites was through the urine, accounting for about 70% of the recovered radioactivity. Metabolism became saturated at 1,000 ppm, since unchanged vinyl chloride increased to 112.3% and urinary radioactivity decreased to 56.3%. At 5,000 ppm, more than half the recovered radioactivity appeared as unchanged vinyl chloride in expired air, and urinary excretion accounted for about 27% of the recovered activity. Generally, there was little change in the proportion of recovered radioactivity excreted in the feces or exhaled as carbon dioxide. The percentage of the radioactivity retained in the carcass and tissues appeared to be somewhat decreased at 5,000 ppm compared with 10 and 1,000 ppm, suggesting preferential retention of metabolites rather than unchanged vinyl chloride. It should be noted that the trend of a greater percentage of vinyl chloride being exhaled at higher concentrations in animals is the opposite of what

was observed in humans in Krajewski et al. (1980). In humans, a higher percentage of unmetabolized vinyl chloride was found in expired air at lower concentrations (Krajewski et al. 1980). However, it is possible that a reversal of this trend would occur in humans if concentrations were increased to those used in the animal studies.

Pulmonary excretion of unaltered vinyl chloride in rats followed first-order kinetics regardless of exposure concentrations, with half-lives of 20.4, 22.4, and 30 minutes following 6-hour exposures at 10, 1,000, and 5,000 ppm, respectively. The urinary excretion of radioactivity was biphasic, with the second or slow phase accounting for less than 3% of the total urinary excretion. Estimated half-lives for the rapid (first-order) phase were 4.6, 4.1, and 4.5 hours, at 10, 1,000, and 5,000 ppm, respectively. Urinary metabolites included N-acetyl-S-(2-hydroxyethyl)cysteine, thiodiglycolic acid, and possibly S-(2-hydroxyethyl)cysteine (Watanabe et al. 1976b). Identification of these metabolites of vinyl chloride in the urine indicates that vinyl chloride is transformed in the body to a reactive metabolite, which is then detoxified by reaction with glutathione (GSH, gamma-glutamylcysteinylglycine). Subsequently the glutamic acid and glycine moieties of the tripeptide are cleaved, and the cysteine conjugate of the reactive metabolite of vinyl chloride is either acetylated or further oxidized and excreted.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to vinyl chloride.

Single oral doses of ^{14}C -vinyl chloride (0.05, 0.25, 1.0, 20, 100, and 450 mg/kg) were administered to rats, and the excretion of radioactivity was monitored over a 72-hour period (Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a). A striking increase in exhalation of unchanged vinyl chloride and compensatory decreases in urinary and fecal excretion of radioactivity and exhalation of carbon dioxide were observed at greater than 20 mg/kg, suggesting that metabolic saturation had occurred at that dosage. At less than 1.0 mg/kg, the predominant route of elimination was urinary excretion of polar metabolites.

Exhalation of unchanged vinyl chloride was generally complete within 3-4 hours, but excretion of metabolites continued for days (Green and Hathway 1975). Pulmonary excretion of vinyl chloride appeared to be monophasic at less than 1.0 mg/kg, with a half-life of about 55-58 minutes (Watanabe

et al. 1976a). At 100 mgkg, pulmonary excretion of vinyl chloride was biphasic, with half-lives of 14.4 and 40.8 minutes for the rapid and slower phases, respectively. Urinary excretion of radioactivity was biphasic, with the rapid phase accounting for more than 97% of total urinary radioactivity and having half-lives of 4.5-4.6 hours for dosages of 0.05-100 mg/kg.

Metabolites identified in the urine of orally treated rats were consistent with the formation of 2-chloroethylene oxide and 2-chloroacetaldehyde (Green and Hathway 1977; Watanabe et al. 1976a), as postulated for metabolism following inhalation exposure. The major metabolites were identified as thiodiglycolic acid and N-acetyl-S-(2-hydroxyethyl)cysteine (Watanabe et al. 1976a). N-Acetyl-S-(2-chloroethyl)cysteine and S-(2-chloroethyl)cysteine have also been identified as having smaller amounts of radiolabelled urea, glutamic acid, and 2-chloroacetic acid (Green and Hathway 1975).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to vinyl chloride.

When two rhesus monkeys received whole-body (except head) exposure to vinyl chloride gas (800 and 7,000 ppm) for 2-2.5 hours, although very little vinyl chloride was absorbed, most was excreted in expired air (Hefner et al. 1975a). The percentages of absorbed vinyl chloride that were exhaled were 0.028% and 0.014% at 700 and 8,000 ppm, respectively (Hefner et al. 1975a).

2.3.4.4 Other Routes of Exposure

The elimination of radioactivity following intraperitoneal administration of ^{14}C -vinyl chloride to rats resembles the pattern observed following inhalation or oral administration. Following an intraperitoneal dose of 0.25 mg/kg, exhalation of unchanged vinyl chloride, exhalation of carbon dioxide, and urinary and fecal excretion of radioactivity accounted for 43.2%, 11 .O%, 43-l%, and 1.8% of the administered dose, respectively (Green and Hathway 1975). At 450 mg/kg, exhaled vinyl chloride increased to 96.2% of the administered dose, carbon dioxide decreased to 0.7%, urinary radioactivity decreased to 2.6%, and fecal radioactivity decreased to 0.1%.

Doses administered intravenously were eliminated very rapidly and almost entirely by exhalation of unchanged vinyl chloride. Green and Hathway (1975) administered a 0.25-mg/kg intravenous dose of

^{14}C -vinyl chloride to rats and recovered 80% of the dose within 2 minutes and 99% within 1 hour as unchanged compound in expired air.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 199Os, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these

differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

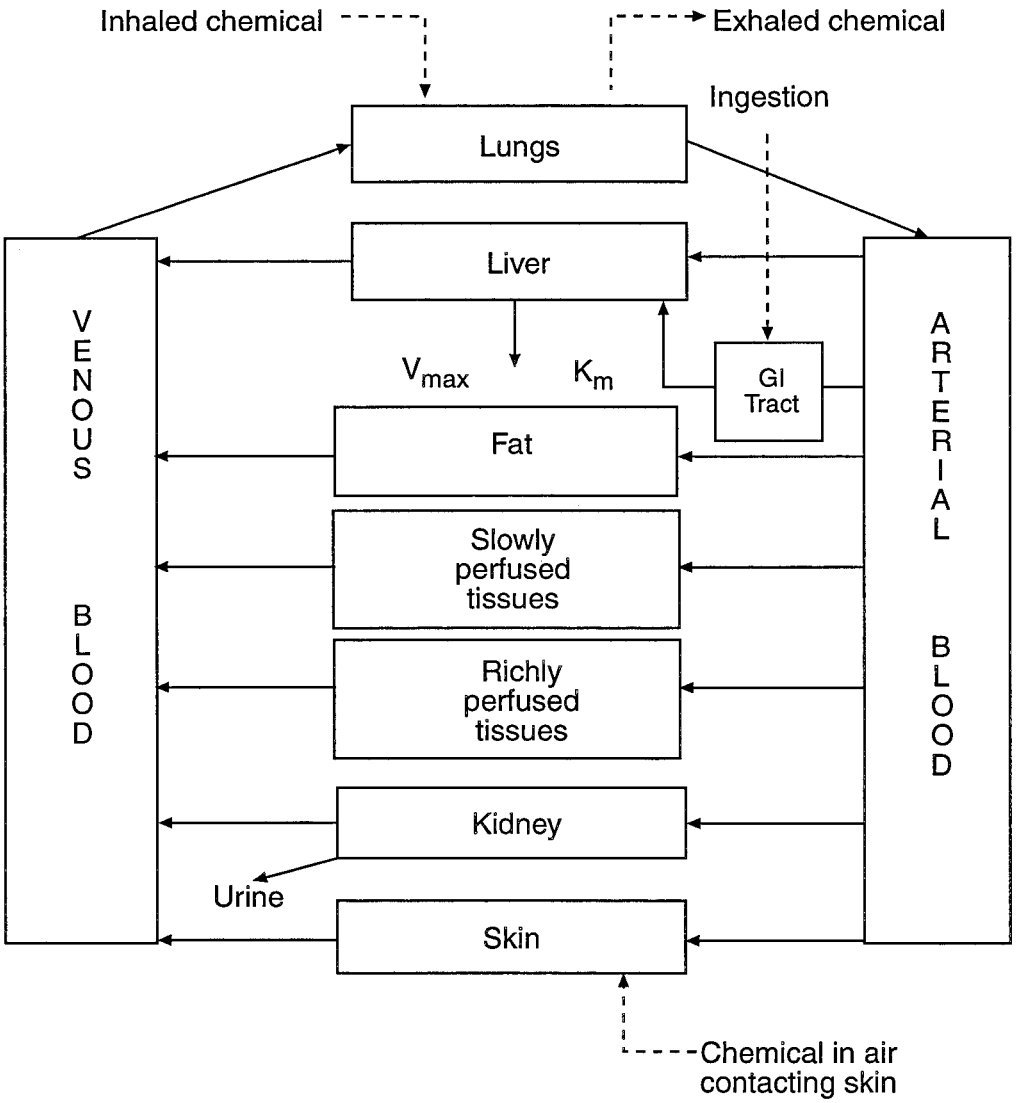
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

If PBPK models for vinyl chloride exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Summary of PBPK/PD Models

Models have been developed to predict the metabolism and distribution of vinyl chloride. EPA (19878) developed a PBPK model to estimate the metabolized dose of vinyl chloride coupled to a multistage model to estimate cancer risk in animals. This PBPK model consists of four compartments, the liver, fat group, highly perfused tissue, and poorly perfused tissue. All metabolism was assumed to occur in the liver by one saturable pathway (Michaelis-Menten Kinetics) and by a first-order metabolism pathway. The physiologic parameters used were values from an EPA draft “Reference Physiologic Parameters in Pharmacokinetic Modeling” by Dr. Curtis Travis of the Oak Ridge National Laboratory. The number of rats predicted to develop liver cancer by the model was similar to that observed in completed studies.

Figure 2-4 Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

The dose delivery of the vinyl chloride model developed by EPA (19878) was further validated by the Air Force (1990b) study with additional vinyl chloride metabolism studies in rats. At low concentrations, this model fit *in vivo* data in rats by Gehring et al. (1978) well, but at concentrations above 25 ppm, the model predicted a greater amount of vinyl chloride metabolism than observed. The Air Force (1990b) then made modifications in the model to improve the fit with actual data. In the first modification, both vinyl chloride and the epoxide metabolite were assumed to react with glutathione. This model had difficulty predicting glutathione depletion at high doses; for example, it predicted glutathione depletions higher than observed at 4,600-5,800 ppm vinyl chloride. The second alternative model, in which only the product of the first-order metabolism was assumed to react with glutathione, also predicted glutathione depletions higher than observed at high concentrations. To improve the model, the investigators suggested the addition of a low-affinity glutathione pathway.

Using data obtained from Wright-Patterson Air Force Base, the Air Force (1990b) extended the first glutathione conjugation model, developed in rats, to different strains of rats, mice, and hamsters. Vinyl chloride gas uptake experiments were completed in which animals were exposed to various concentrations of vinyl chloride in closed chambers for up to 6 hours, and the disappearance of vinyl chloride was monitored. The glutathione content of the animals was also measured immediately after exposure. Using data from these studies and the physiologic parameters shown in Table 2-4, the investigators estimated metabolic parameters for vinyl chloride and the rate constant for the conjugation of vinyl chloride with glutathione (Table 2-5). Using the metabolic parameters determined from the gas uptake experiments, the model predictions showed good agreement with the actual data for all the strains tested. It does not appear that the investigators further validated the model with data from studies other than those used to determine the metabolic parameters. This model was not used to estimate metabolized doses for humans because the investigators indicated that human data to estimate all the required parameters were not available. They suggested that allometry may have to be used to estimate some of the parameters for humans.

Clewell et al. (1995) used PBPK modeling coupled with a linearized multistage model to predict human cancer risk. The model again had four compartments as described for the EPA (19878) study, and the same EPA physiologic parameters were used. Partition coefficients were from *in vitro* experiments and are shown in Table 2-3. Metabolism was modeled by two saturable pathways: one high affinity, low capacity (P450 2El), and one low affinity, high capacity (2C11/6 and lA1/2). The metabolic parameters used were not provided, but they were estimated from the Air Force (199Ob)

TABLE 2-4. Physiological Parameters Used to Estimate Parameters from Vinyl Chloride Gas Uptake Experiments[a]

Parameter	Rats	Mice	Hamsters
Ventilation rate (L/hour/body weight$^{0.74}$)	14	23–25[b]	13
Total cardiac output (L/hour/body weight$^{0.74}$)	14	23–25[b]	13
Blood flow to the liver (fraction of total cardiac output)	0.25	0.24	0.24
Blood flow to highly perfused tissue (fraction of total cardiac output)	0.51	0.52	0.52
Blood flow to fat (fraction of total cardiac output)	0.09[c]	0.05	0.09
Blood flow to poorly perfused tissue (fraction of total cardiac output)	0.15[c]	0.20	0.15
Volume of tissue (L/body weight)	0.04	0.04	0.04
Volume of highly perfused tissue (L/body weight)	0.04	0.05	0.05
Volume of fat tissue (L/body weight)	0.07–0.1[d]	0.04	0.07
Volume of poorly perfused tissue (L/body weight)	0.72–0.75[d]	0.78	0.75

[a]Air Force (1990b); units of body weight were not provided.
[b]Ventilation rates and total cardiac outputs were 23 for male B6C3F$_1$ mice, 25 for female B6C3F$_1$ mice, 28 for female CD-1 mice, and 35 for male CD-1 mice.
[c]Male Wistar rats blood flow to fat = 0.08 and blood flow to slowly perfused tissue = 0.16.
[d]Female F-344 and female Wistar rats had volume of fat tissue = 0.07 and volume of slowly perfused tissue = 0.75; male F-344 and female Wister rats had volume of fat tissue = 0.08 and volume of slowly perfused tissue = 0.74; male Wister and male CDBR rats had volume of fat tissue = 0.1 and volume of slowly perfused tissue = 0.72.

TABLE 2-5. Estimates of Metabolic Parameters Obtained from Gas Uptake Experiments[a]

Species	Strain	Sex	V_{max}/body weight$^{0.7}$ (mg/hour/body weight$^{0.7}$)	Kfc (body weight$^{0.3}$/hour)	Kgsc (body weight$^{0.3}$/hour/μmol/L GSH)
Rat	CDBR	M	2.5	0.63	ND
		F	2.47	1.0	0.000241
	F-344	M	3.17	1.08	0.000249
		F	2.95	1.03	0.000227
	Wistar	M	3.11	0.45	0.000093
		F	2.97	1.55	0.00040
Mouse	$B6C3F_1$	M	5.89	5.5	0.000827
		F	5.53	8.93	0.00167
	CD-1	M	6.99	5.1	0.000563
		F	5.54	6.62	0.000809
Hamster	Golden Syrian	M	4.94	1.67	ND
		F	4.76	2.06	0.000330

[a]Air Force (1990b)

F = female; GSH = glutathione; Kfc = first order of epoxide formation; Kgsc = rate constant for conjugation of vinyl chloride with glutathione; M = male; ND = not determined; V_{max} = maximum velocity of reaction

model. This model assumed that the metabolites (chloroethylene oxide and chloroacetaldehyde) were further degraded to carbon dioxide, or reacted with glutathione, or reacted with DNA. The parameters (not stated) for reactions of the metabolites were estimated from vinylidene chloride data (D'Souza and Andersen 1988) using appropriate allometric scaling. Based on this PBPK model and a linearized multistage model using liver angiosarcoma data from animal studies, the human risk estimates for lifetime exposure to 1 ppb vinyl chloride ranged from 1.1 to 15.7 per million persons (Clewell et al. 1995). Based on the incidence of liver angiosarcoma in human epidemiological studies, the risk estimates for lifetime exposure to 1 ppb vinyl chloride were 0.4-4.22 per million persons. Clewell et al. (1995) indicated that the risk estimates using PBPK modeling are about 30-50 times lower than estimates using external dose calculations based on the linearized multistage model.

Reitz et al. (1996) also developed a PBPK model that coupled measures of delivered dose in rats to a linearized multistage model to predict the incidence of hepatic angiosarcoma in mice and humans. The model incorporated four compartments - fat, muscle, rapidly perfused tissues, and liver. Physiological parameters in the model were based on similar ones used in an earlier multispecies PBPK model developed for methylene chloride. Partition coefficients were estimated by vial equilibration techniques similar to those described in the Air Force (1990b) study. Metabolic rate constants were obtained from *in vivo* gas uptake experiments performed at WrigRt-Patterson Air Force Base.

Based on the PBPK-based procedure utilized by Reitz et al. (1996), the predicted human risk estimates ranged from about 200 cases per 100,000 (for workers employed 10 years at a plant where the TWA was 50 ppm) to almost 4,000 cases per 100,000 in workers employed for 20 years in a plant where the TWA was 2,000 ppm. The predictions of human risk were compared with the data reported by Simonato et al. (1991). The predictions of angiosarcoma incidence in humans were almost an order of magnitude higher than actually observed in exposed human populations, and were more than two orders of magnitude lower than risk estimations that did not utilize pharmacokinetic data.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Vinyl chloride appears to be rapidly and completely absorbed following inhalation and oral exposure (Bolt et al. 1977; Krajewski et al. 1980; Watanabe et al. 1976a; Withey 1976). No information was located regarding the mechanism of absorption Distribution of vinyl chloride in the body is rapid and widespread. Storage is limited by rapid metabolism and excretion (Bolt et al. 1976a). The primary route of excretion of metabolites of vinyl chloride is through urine. Urinary metabolites that have been identified include N-acetyl-S-(2-hydroxyethyl)cysteine, thiodiglycolic acid, and possibly S-(2-hydroxyethyl)cysteine (Watanabe et al. 1976b). The presence of these metabolites indicates that vinyl chloride undergoes transformation to a reactive metabolite, which is subsequently detoxified by a reaction with glutathione. The glutamic acid and glycine moieties of the tripeptide are cleaved, and the cysteine conjugate of the reactive metabolite is either acetylated or further oxidized and excreted. Exhalation of unmetabolized vinyl chloride is not an important pathway of elimination by humans after exposure to low concentrations. The importance of exhalation of vinyl chloride varies with the exposure concentration. At low exposure concentrations, little vinyl chloride is excreted unchanged in exhaled air. However, vinyl chloride can be excreted unchanged in exhaled air if metabolic pathways become saturated at high exposure concentrations (Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a, 1978a).

2.4.2 Mechanisms of Toxicity

The mechanisms of toxicity for noncancer effects of vinyl chloride have not been completely elucidated. Vinyl chloride disease exhibits many of the characteristics of autoimmune diseases (Raynaud’s phenomenon and scleroderma). B-cell proliferation, hyperimmunoglobulinemia, and complement activation, as well as increased circulating immune complexes or cryoglobulinemia have been noted in affected workers, indicating stimulation of immune response (Bogdanikowa and Zawilska 1984; Grainger et al. 1980; Ward 1976). Mechanisms for the vascular changes, such as those occurring with Raynaud’s phenomenon, have been proposed by Grainger et al. (1980) and Ward (1976). According to these mechanisms, a reactive vinyl chloride intermediate metabolite, such as 2-chloroethylene oxide or 2-chloroacetaldehyde, binds to a protein such as IgG. The altered protein initiates an immune response, with deposition of immune products along the vascular endothelium.

Circulating immune complexes are proposed to precipitate in response to exposure to the cold, and these precipitates are proposed to cause blockage of the small vessels. Resorptive bone changes in the fingers, also characteristic of vinyl chloride disease, may be due to activation of osteoclast secondary to vascular insufficiency in the finger tips, but this mechanism has not been conclusively demonstrated.

It has been hypothesized that cardiac arrhythmia reported after vinyl chloride exposure may result from sensitization of the heart to circulatory catecholamines, as occurs with other halogenated hydrocarbons. However, the mechanism for these effects has not been elucidated.

Peripheral nervous system symptoms such as paresthesia, numbness, weakness, warmth in the extremities, and pain in the fingers have been reported after vinyl chloride exposure (Langauer-Lewowicka et al. 1983; NIOSH 1977; Suciu et al. 1963, 1975). It is not known whether these effects represent direct toxic effects of vinyl chloride on peripheral nerves or whether they are associated with tissue anoxia due to vascular insufficiency.

Vinyl chloride is a known human and animal carcinogen. It has been associated with both an increased incidence of hepatic angiosarcomas and hepatotoxicity. The mechanism for these liver effects has been studied to some extent. It is believed that a reactive epoxide intermediate of vinyl chloride, 2-chloroethylene oxide, interacts directly with DNA and produces alkylation products such as 3,p-ethenocytidine, l,N6-ethenoadenosine, and 7,N-(2-oxoethyl)-guanosine (Fedtke et al. 1990; Swenberg et al. 1992). This alkylation results in a highly efficient base-pair substitution that leads to neoplastic transformation. The epoxide intermediate is formed when vinyl chloride is oxidized by the P-450 isoenzymes. There also is evidence of the mutagenicity of 2-chloroacetaldehyde in cultured human fibroblast cells (Matsuda et al. 1995).

The mechanisms for clastogenic effects of vinyl chloride exposure were examined by Fucic et al. (1990). Since chromatid and bichromatid breaks most frequently occurred in the terminal A, B, and C group chromosomes, these investigators suggested that vinyl chloride or its metabolites might interact with specific sites along the chromosome. This implies that the carcinogenicity of vinyl chloride can be explained in part by its nonrandom interaction with particular genes.

2.4.3 Animal-to-Human Extrapolations

Limited information is available regarding the toxicokinetic differences between species.

Toxicokinetic data in humans are limited (Krajewski et al. 1980; Sabadie et al. 1980), but a primate study suggested that metabolism may saturate at lower concentrations in primates than in rats (Buchter et al. 1980), which is suggestive of a lower saturation point in humans. Exposure concentrations greater than about 3OOAOO ppm in the primate study showed saturation characteristics (Buchter et al. 1980).

Correlation of toxic effects between humans and animals with regard to respiratory, cardiovascular, hematological, hepatic, dermal, immunological, neurological, reproductive, and cancer effects has been noted. Renal effects, including increased relative kidney weight and an increase in severity of tubular nephrosis, have been reported in several rat studies (Bi et al. 1985; Feron and Kroes 1979; Feron et al. 1979a), but no evidence of renal effects has been shown in humans. Thus, it is unclear whether the renal effects reported in rats represent a lesion that can be attributed to vinyl chloride exposure that is unique to rats or whether the effects represent an increase in severity of a naturally occurring lesion. From the limited data available, however, it does not appear that the rat is the most appropriate species for use in studies of renal toxicity.

2.5 RELEVANCE TO PUBLIC HEALTH

The major route of exposure to vinyl chloride by humans living near hazardous waste sites is via inhalation. Vinyl chloride may be present in ambient air near hazardous waste sites as a result of its volatilization from leaks in storage containers, or from contaminated soil or water. Vinyl chloride can also be produced by the anaerobic dehalogenation of tetrachloroethylene and trichloroethylene (Smith and Dragun 1984). Oral exposure to vinyl chloride via ingestion of contaminated water may also occur. Dermal exposure to liquid vinyl chloride is highly unlikely because of its low boiling point (-13.4°C). However, vinyl chloride is generally transported as a liquid in pressurized containers, and puncture of such a container at a hazardous waste site could result in brief exposure of the skin to liquid vinyl chloride, although this is unlikely. It is more likely that dermal exposure to vinyl chloride would occur through domestic bathing or showering using contaminated groundwater, but the levels in groundwater would probably be low. Dermal exposure to gaseous vinyl chloride may also occur, but

a study using rats indicated that absorption of vinyl chloride across the skin is very limited (Hefner et al. 1975a).

Additional sources of potential exposure not directly related to living near hazardous waste sites, but which may also apply in such cases, include inhalation of emissions from vinyl chloride production or PVC manufacturing facilities (up to 1 ppm) (EPA 1979a, 1982f; Fishbein 1979; Gordon and Meeks 1977), ingestion of water contaminated as a result of the leaching of vinyl chloride from PVC pipes (up to 0.0014 ppm) (Dressman and McFarren 1978), or ingestion of foods contaminated as a result of vinyl chloride leaching from PVC products used in food production or storage (up to 98 ppm) (Benfenati et al. 1991; Gilbert et al. 1980; Williams 1976; Williams and Miles 1975). However, almost no migration of vinyl chloride from PVC into food was predicted in a modeling study of food packaging and storage at very low concentrations of vinyl chloride (Kontominas et al. 1985). In addition, the FDA now regulates the amount of vinyl chloride in PVC products that may be available to leach into foods; thus this mode of exposure is likely to be negligible.

With a vapor density of 2.15, in areas of high concentration vinyl chloride vapor tends to disperse slowly, collecting in low spots such as ditches (Fire 1986). In low concentrations such as those expected near hazardous waste sites, it will qluickly be dispersed into the atmosphere. Dispersion models exist that can be used to calculate the airborne concentration of vinyl chloride in the vicinity of hazardous waste sites.

The effects that have been reported to occur in humans in response to vinyl chloride exposure come almost exclusively from studies of workers exposed by inhalation in the workplace. Because women traditionally have not been employed in PVC-manufacturing positions in North America and Western Europe, most of the data on humans from these areas concerns effects in males. Also, virtually all of the epidemiological studies are limited by the absence of data on the actual levels to which workers were exposed. However, studies in animals by the inhalation and oral routes provide an indication of the doses of vinyl chloride that may be associated with these effects.

Acute high-level exposure of humans to vinyl chloride is associated with the development of signs of intoxication such as dizziness, drowsiness, and/or headache. Reports from vinyl chloride workers and studies in animals indicate that loss of consciousness may also be associated with exposure to very high levels. Two deaths connected with occupational exposure to vinyl chloride have been reported.

Autopsy results from these men as well as autopsy results from animals dying from extremely highlevel exposures indicate that levels of vinyl chloride producing death may cause lung and kidney irritation and inhibition of blood clotting. Cardiac arrhythmias have also been reported in animals as a result of acute exposure to very high levels of vinyl chloride (Carr et al. 1949; Oster et al. 1947). However, because these effects have not been reported in humans after exposure to high concentrations of vinyl chloride, it appears unlikely that persons exposed to low levels of vinyl chloride will experience these effects.

Longer term exposure of humans in occupational settings has been associated with the development of a number of other toxic effects. However, exposure levels in these studies are generally not quantified, and thresholds for the effects have not been identified. Histopathological changes characteristic of vinyl chloride exposure have been reported to take place in the liver. These changes include extensive fibrosis of the portal tracts and septa, and intralobular perisinusoidal regions, hepatocellular degeneration, sinusoidal dilation, and hypertrophy and hyperplasia of both hepatocytes and sinusoidal cells (Falk et al. 1974; Gedigke et al. 1975; Marsteller et al. 1975; Popper and Thomas 1975; Tamburro et al. 1984). These changes in liver structure develop in the absence of overt symptoms of liver toxicity, and standard biochemical measures of liver function have been of little value in detecting them (Liss et al. 1985). Reports indicate that peripheral neuropathy may also develop in some workers occupationally exposed to vinyl chloride (Lilis et al. 1975; Perticoni et al. 1986; Sakabe 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976). In addition, toxic effects on male reproductive function may occur (Bi et al. 1985; Short et al. 1977; Suciu et al. 1975; Veltman et al. 1975; Walker 1976). Studies in animals indicate that vinyl chloride may cause fetal resorptions, delayed development, and an increased incidence of the soft tissue anomaly, dilated ureter (John et al. 1977, 1981; Ungvary et al. 1978). When animals were exposed in *utero,* some changes in liver function were observed during adolescence (Mirkova et al. 1978). However, similar results have not been confirmed in humans.

A syndrome referred to as vinyl chloride disease has been observed in a small percentage of vinyl chloride workers, many of whom were employed as polymerization tank cleaners. This job exposed workers to very high levels of vinyl chloride. Vinyl chloride disease is very similar to systemic sclerosis and includes some or all of the following symptoms: Raynaud’s phenomenon (fingers blanch and numbness and discomfort are experienced upon exposure to the cold) (LaPlanche et al. 1987, 1992; Lilis et al. 1975; Marsteller et al. 1975; Ostlere et al. 1992; Suciu et al. 1963, 1975; Veltman et

al. 1975; Walker 1976), acroosteolysis (resorption of the terminal bones of the fingers and/or toes) (Dinman et al. 1971; Lilis et al. 1975; Marsteller et al. 1975; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967), joint and muscle pain (Lilis et al. 1975), enhanced collagen deposition (Harris and Adams 1967; Markowitz et al. 1972; Ostlere et al. 1992; Veltman et al. 1975), decreased elasticity (Lilis et al. 1975), and scleroderma-like skin changes (Jayson et al. 1976). A few studies showed that Raynaud's phenomenon may gradually disappear upon removal from exposure (Freudiger et al. 1988; Suciu et al. 1963, 1975). Bone resorption has continued after cessation of exposure in some cases (Markowitz et al. 1972; Preston et al. 1976), but not in all cases (Veltman et al. 1975; Wilson et al. 1967). Studies in animals support the findings observed in humans (Viola 1970). In addition, renal nephrosis has been reported to occur in animals exposed to vinyl chloride, but similar results have not been confirmed in humans (Feron and Kroes 1979).

Studies in both humans and animals indicate that vinyl chloride is carcinogenic. Hepatic angiosarcoma has been identified in workers exposed to vinyl chloride by the inhalation route (Byren et al. 1976; Creech and Johnson 1974; Fox and Collier 1977; Infante et al. 1976b; Jones et al. 1988; Laplanche et al. 1992; Monson et al. 1975; Pirastu et al. 1990; Rinsky et al. 1988; Simonato et al. 1991; Teta et al. 1990; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989). Also, there are some studies that indicate that cancers of the central nervous system (Cooper 1981; Monson et al. 1975; Waxweiler et al. 1976; Wong et al. 1991), respiratory tract (Belli et al. 1987; Infante et al. 1976b; Monson et al. 1975; Waxweiler et al. 1976), and lymphatic and hematopoietic systems (Monson et al. 1975; Rinsky et al. 1988; Smulevich et al. 1988; Weber et al. 1981) may occur in humans following inhalation exposure. Studies in a variety of species exposed by both the inhalation and oral routes show an increased incidence of hepatic angiosarcoma (Bi et al. 1985; Feron et al. 1981; Maltoni and Cotti 1988; Maltoni et al. 1981). Therefore, it is appropriate to consider that vinyl chloride is carcinogenic by the oral route as well.

Minimal Risk Levels for Vinyl Chloride

Inhalation MRLs

Studies in humans did not provide sufficient data regarding exposure levels and their correlation with observed effects. Therefore animal studies were used for the derivation of MRLs.

- An acute-duration inhalation MRL of 0.5 ppm was derived from a NOAEL of 50 ppm for developmental effects in mice exposed 7 hours/day from gestational days 6 to 15 (John et al. 1977, 1981). No adverse maternal or fetal effects were noted at 50 ppm, except a slight increase in fetal crown-rump length that was not observed at 500 ppm. Adjustment for intermittent exposure was not performed because vinyl chloride readily reaches steady state, is rapidly metabolized and excreted, and neither it nor its metabolites tend to accumulate. The NOAEL was converted to a Human Equivalent Concentration and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

- An intermediate-duration inhalation MRL of 0.03 ppm was derived from a LOAEL value of 10 ppm for increased relative liver weight in rats (Bi et al. 1985). The dose was not adjusted for intermittent exposure because vinyl chloride readily reaches steady state, is rapidly metabolized and excreted, and neither it nor its metabolites tend to accumulate. The LOAEL was converted to a Human Equivalent Concentration and divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). Increased relative liver weight (Sokal et al. 1980; Torkelson et al. 1961) and adverse histopathological changes (Lester et al. 1963; Schaffner 1978; Sokal et al. 1980; Wisniewska-Knypl et al. 1980) have been observed in several otlrer intermediate-duration inhalation studies. The study by Bi et al. (1985) shows hepatotoxicity (increased relative liver weight) at exposure levels slightly lower than those of other studies. Additional support for the selection of 10 ppm as the lowest LOAEL comes from other organ weight changes observed by Bi et al. (1985) at 10 ppm and from another study demonstrating immunostimulation at 10 ppm (Sharma and Gehring 1979).

No chronic-duration inhalation MRL was derived for vinyl chloride because of the absence of a suitable LOAEL or NOAEL for derivation. The lowest LOAEL (100 ppm) from a chronic-duration study was for a serious end point (testicular necrosis) in a rat toxicity study (Bi et al. 1985). MRLs are not derived using serious end points. In addition, carcinogenicity was observed at concentrations equal to and less than 100 ppm (Bi et al. 1985; Drew et al. 1983; Lee et al. 1978; Maltoni et al. 1981).

Oral MRLs

Studies in humans did not provide sufficient data regarding exposure levels and their correlation with observed effects. Therefore animal studies were used for the derivation of MRLs.

- A chronic-duration oral MRL of 0.00002 mg/kg/day was derived from a LOAEL value of 0.018 mg/kg/day for an increased incidence of basophilic foci of cellular alteration in the livers of rats (Til et al. 1983, 1991). The MRL value was obtained by dividing the LOAEL by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). The selection of this end point is supported by an earlier study from the same laboratory (Feron et al. 1981) that showed increased areas of cellular alteration consisting of clear foci, basophilic foci, and eosinophilic foci in the liver of rats at the lowest dose tested (1.8 mg/kg/day). An increased incidence of hepatic cysts was found in female rats fed 1.7 mg/kg/day in the Til et al. (1983, 1991) studies.

No acute- or intermediate-duration oral MRLs were derived for vinyl chloride because of an absence of data on the effects of oral exposure to vinyl chloride for these duration categories.

Death. Vinyl chloride, at sufficiently high levels, may be fatal to humans following inhalation exposure. The autopsy report by Danziger (1960) regarding the deaths of two vinyl chloride workers showed congestion of the internal organs, particularly the kidneys and lungs, and failure of the blood to clot, but did not estimate the levels to which these workers had been exposed. Inhalation exposure of animals for as brief a period as 30 minutes to concentrations of vinyl chloride ranging from 100,000 to 400,000 ppm have been reported to be lethal to rats, mice, and guinea pigs (Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930). The cause of death was attributed to respiratory failure secondary to central nervous system depression in one study (Lester et al. 1963). However, reports of cardiac arrhythmicity at similar levels (Carr et al. 1949; Oster et al. 1947) suggest that cardiac arrest may have contributed to the deaths. The levels of vinyl chloride found to cause death in animals are extremely high and unlikely to exist under most environmental conditions (with the exception of concentrated emissions from a large point source). However, increased mortality was observed in pregnant mice when they were exposed to 500 ppm for 10 days during gestation (John et al. 1977, 1981). Therefore, it is possible that pregnancy might increase the susceptibility to the effects of vinyl chloride. Because of the limited solubility of vinyl chloride in water, acute ingestion of a lethal dose

of vinyl chloride in contaminated water is improbable. Thus, it is unlikely that acute exposure to low levels of vinyl chloride in the air or water near hazardous waste sites will cause death.

No increase in mortality was noted in a prospective cohort study of 1,100 workers exposed to vinyl chloride compared to the controls (Laplanche et al. 1992). Longer term, low-level exposures have been associated with decreased survival in a number of animal inhalation exposure studies (Adkins et al. 1986; Drew et al. 1983; Feron et al. 1979a; Hong et al. 1981; Lee et al. 1978; Viola 1970) and oral exposure studies (Feron et al. 1981; Til et al. 1983, 1991). Decreased survival of rats and mice was observed at inhalation exposures as low as 50 ppm for 6 hours per day, 5 days per week, for up to 10 months (Hong et al. 1981) and oral exposures as low as 1.7 mg/kg/day over the course of a lifetime (Til et al. 1983, 1991). The decreased survival noted in these studies may be a reflection of increased mortality due to cancer induction by vinyl chloride.

The significance of a shortened lifespan in animals following low-level chronic exposure with regard to potential adverse effects in humans is unknown.

Systemic Effects

Respiratory Effects. Both autopsy reports from workers with vinyl chloride-related deaths (Danziger 1960) and animal studies using extremely high levels of vinyl chloride (100,000 ppm and above) (Lester et al. 1963; Mastromatteo et al. 1960) indicate that such levels of vinyl chloride cause respiratory irritation by the inhalation route. It is unlikely that respiratory irritation will result from exposure to low levels of vinyl chloride in the air near hazardous waste sites.

Studies of workers who have been occupationally exposed to vinyl chloride give mixed results regarding the chronic respiratory effects of vinyl chloride. Gamble et al. (1976), Laplanche et al. (1987), and NIOSH (1977) reported no adverse respiratory effects associated with occupational vinyl chloride exposure. However, other investigators found increased incidences of emphysema, decreased respiratory volume and vital capacity, respiratory insufficiency, decreased respiratory oxygen and carbon dioxide transfer, pulmonary fibrosis, and abnormal chest x-rays (Lilis et al. 1975, 1976; Lloyd et al. 1984; Suciu et al. 1975; Walker 1976; Wong et al. 1991). Factors that may confound the interpretation of these results include a smoking history and exposure to PVC resin dust or to other chemicals.

Histopathologic examination of rats and mice exposed to vinyl chloride for periods of 6 months or a year provide some supportive evidence for the respiratory pathology associated with high-level exposure (2,500, 5,000, or 30,000 ppm) (Feron and Kroes 1979; Suzuki 1978, 1980, 1981; Viola et al. 1971). These studies have identified changes such as proliferation and hypertrophy of the bronchiolar epithelium, hypersecretion of mucin, hyperplasia of the alveolar epithelium, mobilization of alveolar macrophages, increased pulmonary hemorrhages, and interstitial pneumonia.

Cardiovascular Effects. A small percentage of workers exposed to vinyl chloride develop vinyl chloride disease. One of the symptoms of this disease is a condition referred to as Raynaud's phenomenon, in which the fingers blanch and feel numb and uncomfortable upon exposure to the cold. Arteriography and biopsy material from afflicted workers indicate that exposure to vinyl chloride may cause blockage of the blood vessels supplying the hand, hypervascularity, and a thickening of the blood vessel walls (Harris and Adams 1967; Preston et al. 1976; Veltman et al. 1975; Walker 1976).

Vinyl chloride disease has been reported to be an autoimmune response similar to systemic sclerosis. Mechanisms for the vascular effects proposed by Grainger et al. (1980) and Ward (1976) relate the vascular response to the immunologic changes observed in these workers. According to these mechanisms, a reactive vinyl chloride intermediate metabolite, such as 2-chloroethylene oxide or 2-chloroacetaldehyde, binds to a protein such as IgG. The altered protein initiates an immune response, with deposition of immune products along the vascular endothelium. Circulating immune complexes are proposed to precipitate in response to exposure to the cold, and these precipitates are proposed to cause blockage of the small vessels.

Studies in rodents exposed by inhalation to high levels of vinyl chloride have reproduced these symptoms to some extent. Thickening of the arterial vessel walls has been observed in rats exposed to high concentrations of vinyl chloride for a year (Feron and Kroes 1979; Viola 1970). Threshold levels for the production of this effect have not been determined. However, because of the appearance of Raynaud's phenomenon only in workers with exposure to very high levels of vinyl chloride, it is presumed unlikely that persons exposed to low levels of vinyl chloride near hazardous waste sites would be affected.

Limited data are available regarding cardiovascular-related deaths in humans (Byren et al. 1976); however, cardiac arrhythmias have been produced in dogs exposed by inhalation to extremely high

levels of vinyl chloride (Carr et al. 1949; Oster et al. 1947). It is unlikely that persons exposed to low levels of vinyl chloride in the air or water near hazardous waste sites will develop cardiac rhythm abnormalities.

Gastrointestinal Effects. Although gastrointestinal effects such as gastritis and ulcers were reported in vinyl chloride workers, the significance of these effects is not known because no unexposed workers were used as controls (Lilis et al. 1975). Other effects that have been reported, such as nausea, were found in workers who had been selected based upon liver dysfunction (Ho et al. 1991). Based upon the limited data available, it appears unlikely that persons exposed to low levels of vinyl chloride near hazardous waste sites would experience gastrointestinal effects.

Hematological Effects. The blood of both humans and animals that died as a result of acute exposure to extremely high levels of vinyl chloride did not clot (Danziger 1960; Mastromatteo et al. 1960). Slight-to-severe thrombocytopenia has been observed in vinyl chloride workers in several (Marstellar et al. 1975; Micu et al. 1985; Veltman et al. 1975), but not all (Lilis et al. 1975), studies. However, studies in animals using nonlethal concentrations of vinyl chloride have indicated that such levels result in a decreased clotting time. In a study by Feron et al. (1979a), a decrease was observed in the time necessary for blood to clot in rats exposed to 5,000 ppm for 1 year. However, the statistical significance of these effects was not reported. A decreased clotting time was observed in rats whose oral intake of vinyl chloride in the diet was 17 mg/kg/day for 2 years (Feron et al. 1981). Mean prothrombin time was decreased to about 39 seconds in treated animals compared to about 41.5 seconds in controls after either 26 or 52 weeks (Feron et al. 1981). Thus, it is uncertain whether persons exposed to low levels of vinyl chloride near hazardous waste sites would experience abnormal clotting times.

Musculoskeletal Effects. Another characteristic of vinyl chloride disease is acroosteolysis, in which the terminal phalanges of the fingers are resorbed. Acroosteolysis in vinyl chloride workers was observed to be preceded by Raynaud's phenomenon in most instances (Dinman et al. 1971; Freudiger et al. 1988; Harris and Adams 1967; Magnavita et al. 1986; Markowitz et al. 1972; Preston et al. 1976; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967). It is unclear whether the resorptive bone changes are due to activation of osteoclasts secondary to vascular insufficiency in the finger tips. Because acroosteolysis was observed exclusively in workers with very high levels of exposure, it is

unlikely that persons exposed to low levels of vinyl chloride near hazardous waste sites would be affected.

Hepatic Effects. Changes in the liver have been observed in humans exposed to vinyl chloride via inhalation. The characteristic pattern of changes consists of hypertrophy and hyperplasia of hepatocytes and sinusoidal cells; sinusoidal dilation associated with damage to the cells lining the sinusoids and/or sinusoidal occlusion associated with crowding due to cellular hypertrophy and hyperplasia; focal areas of hepatocellular degeneration due to disruption of hepatic circulation; and fibrosis of portal tracts, septa, and intralobular perisinusoidal regions (Falk et al. 1974; Gedigke et al. 1975; Marsteller et al. 1975; Popper and Thomas 1975; Popper et al. 1981; Tamburro et al. 1984). These findings are supported by studies in animals (Popper et al. 1981; Sokal et al. 1980; Torkelson et al. 1961). The primary difference between effects observed in animals and humans was the greater degree of fibrosis (reticulin and collagen deposition) in human liver tissue. Structural changes occurred in the livers of humans and animals with little or no change in serum hepatic enzyme activities (Berk et al. 1975; Marsteller et al. 1975; Tamburro et al. 1984; Vihko et al. 1984), although gamma-glutamyl transferase was found to be increased in workers in one study (Du et al. 1995). This was probably due to the limited scope of the necrotic changes. An intermediate-duration inhalation MRL was derived based on hepatic toxicity in male rats observed in a study by Bi et al. (1985).

Acute degenerative changes were also seen in the livers of animals that inhaled extremely high levels of vinyl chloride (Mastromatteo et al. 1960), but it is unlikely for persons briefly exposed to low levels of vinyl chloride near hazardous waste sites to develop similar degenerative changes.

Hepatotoxicity has also been observed in chronic oral studies. Areas of cellular alteration and necrosis were observed in rats orally exposed to vinyl chloride (Feron et al. 1981; Til et al. 1983, 1991). A chronic-duration oral MRL was derived based on tRe hepatic toxicity observed in the Til et al. (1983, 1991) study. Based on the above data, it would be prudent to consider that persons exposed to low levels of vinyl chloride in the air or in contaminated water at hazardous waste sites over long periods of time may develop similar hepatic changes.

Renal Effects. No evidence of human renal disease has been reported in studies of workers occupationally exposed to vinyl chloride. However, increased severity of tubular nephrosis and increased kidney-to-body-weight ratios were observed in rats exposed to concentrations of vinyl

chloride ranging from 100 to 5,000 ppm for periods of up to a year (Bi et al. 1985; Feron and Kroes 1979; Feron et al. 1979a). It is unclear whether the effects observed in rats represent an increase in severity of naturally occurring tubular nephrosis in rats, or whether these effects represent a lesion attributable to the toxic effects of vinyl chloride on the kidney. Thus, insufficient data are available to predict whether persons exposed to low levels of vinyl chloride over long periods may develop renal toxicity.

Endocrine Effects. One study of workers exposed to vinyl chloride found a thyroid insufficiency in most of those with scleroderma (Suciu et al. 1963). Thyroid changes were also noted in rats exposed to high levels of vinyl chloride for 1 year (Viola 1970). In guinea pigs, no histopathological changes in the adrenal glands were reported after an acute exposure to 400,000 ppm (Mastromatteo et al. 1960). Insufficient data are available to predict accurately whether exposure to low levels of vinyl chloride may cause endocrine effects in humans living near hazardous waste sites, but based on results obtained in animal studies, it is unlikely.

Dermal Effects. The third most common characteristic of vinyl chloride disease that was identified in persons with exposure to very high levels of vinyl chloride (such as polymerization tank cleaners) is thickening of the subepidermal layer of the skin. The changes in the skin may appear as maculae above the joints of the fingers or rope-like bundles on the hands and forearms (Lilis et al. 1975; Marsteller et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976). Analysis of biopsied tissue indicates that the thickening is due to increased synthesis and deposition of collagen (Jayson et al. 1976). In most cases, the skin changes are also preceded by Raynaud's phenomenon. Thickening of the skin and increased collagen content have been reproduced to some extent in rats administered high concentrations of vinyl chloride by gavage (Knight and Gibbons 1987). Based on the appearance of this effect predominantly in persons with exposure to very high levels of vinyl chloride, it is unlikely that low-level exposures near hazardous waste sites would cause similar effects.

Ocular Effects. Local bums on the conjunctiva and cornea were observed in a man who died after exposure to an unknown quantity of vinyl chloride vapor escaping from an open valve (Danziger 1960). However, ocular effects have not been observed either in other workers or in animals (Mastromatteo et al. 1960) exposed to high concentrations of vinyl chloride in test chambers. It is unlikely that ocular effects will occur in persons exposed to low levels of vinyl chloride in the air near hazardous waste sites.

Body Weight Effects. Workers who had been intoxicated by vinyl chloride were reported to have experienced anorexia (Suciu et al. 1963, 1975), but no consistent changes in body weight were reported in rats exposed to up to 50,000 ppm for acute durations (Hehir et al. 1981; Kudo et al. 1990). No changes in body weight were reported in rats, mice, or rabbits exposed to 200 or 1,000 ppm vinyl chloride for up to 6 months (Sharma and Gehring 1979; Torkelson et al. 1961). Body weight changes were noted in rats exposed to either 50 ppm vinyl chloride (10 months, 5 days per week, 5 hours per day) or 5,000 ppm vinyl chloride (4-52 weeks, 5 days per week, 7 hours per day) (Feron et al. 1979a; Sokal et al. 1980). Maternal body weight gain was significantly decreased in mice exposed to 500 ppm during gestation days 6-15 (John et al. 1977, 1981). Thus, it appears that there might be some change in body weight associated with vinyl chloride exposure; however, data are not adequate to draw this conclusion with certainty.

Immunological and Lymphoreticular Effects. Increased levels of circulating immune complexes and immunoglobulins have been observed in vinyl chloride workers indicating a stimulatory effect of vinyl chloride on the immune system (Bogdanikowa and Zawilska 1984). Increased percentages of lymphocytes have also been noted in exposed workers (Fucic et al. 1995).

When workers with vinyl chloride disease were examined, a correlation between the severity of the symptoms of vinyl chloride disease (Raynaud's phenomenon, acroosteolysis, joint and muscle pain, enhanced collagen deposition, stiffness of the hands, scleroderma-like skin changes) and the magnitude of the immune response was observed (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976). The most frequent immunologic findings in workers with vinyl chloride disease were an increase in circulating immune complexes and cryoglobulinemia. As the severity of the clinical signs of vinyl chloride disease increased, there was an increase in B-cell proliferation, hyperimmunoglobulinemia, and complement activation.

Because of the similarity of vinyl. chloride disease with the proposed autoimmune disease, systemic sclerosis, and the association of many autoimmune diseases with certain inherited genetic characteristics, the HLA phenotypes of vinyl chloride workers both with and without vinyl chloride disease were examined (Black et al. 1983, 1986). The study authors determined that susceptibility to vinyl chloride disease was increased in the presence of the HLA-DR5 allele or a gene in linkage disequilibrium with it, and progression of the disease to its more severe forms was favored by HLADR3 and HLA-B8.

Stimulation of the immune response has been observed in mice exposed to low-to-moderate levels of vinyl chloride via inhalation for several weeks (Sharma and Gehring 1979). Thus, it may be possible for persons exposed to low levels of vinyl chloride in the air or water near hazardous waste sites to develop immune stimulation. The threshold for developing an autoimmune response in susceptible persons is unknown.

Neurological Effects. Central nervous system depression is the earliest symptom associated with acute high-level vinyl chloride exposure in humans and animals. Concentrations as low as 8,000 ppm may cause dizziness in humans exposed by inhalation (Lester et al. 1963). Workers exposed to vinyl chloride before occupational standards were made more rigorous, complained of dizziness, drowsiness, euphoria, nausea, headache, and occasional loss of consciousness (Ho et al. 1991; Langauer-Lewowicka et al. 1983; Lilis et al. 1975; Marsteller et al. 1975; NIOSH 1977; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976). These symptoms were most frequently experienced by those employed in positions with the greatest exposure to vinyl chloride (cleaners of the autoclaves used to synthesize PVC).

A state of unconsciousness was produced in animals acutely exposed via inhalation to concentrations of approximately 100,000 ppm (Jaeger et al. 1974; Mastromatteo et al. 1960). It is unlikely that exposure to low levels of vinyl chloride in air or water near hazardous waste sites would cause central nervous system depression.

Reports by Magnavita et al. (1986) and Perticoni et al. (1986) suggest that peripheral nerve damage may occur in occupationally exposed workers. Chronic inhalation exposure of animals to high levels of vinyl chloride caused nerve damage and cerebellar degeneration (Viola 1970; Viola et al. 1971). However, threshold levels for this effect are unknown, but it is unlikely that persons exposed to low levels of vinyl chloride in air or water near hazardous waste sites would experience nerve damage.

Reproductive Effects. Studies in humans indicate that the male reproductive function may be adversely affected by exposure to vinyl chloride. Decreased androgen levels have been found in workers occupationally exposed to vinyl chloride (Walker 1976). Also, workers Rave complained of impotency and decreased libido (Suciu et al 1975; Veltman et al. 1975; Walker 1976). These findings are supported by histopathological evidence of testicular damage (Bi et al. 1985; Sokal et al. 1980) and decreased male fertility (Short et al. 1977) in rats exposed by inhalation.

Fewer studies have reported the effects of vinyl chloride on the reproductive function in females. Reduced hemoglobin levels during pregnancy and an increased incidence of elevated blood pressure and edema during pregnancy (preeclampsia) have been observed by Bao et al. (1988). Studies designed to examine these effects in animals were not located. At present, it is unclear whether adverse reproductive effects could occur in persons exposed to low levels of vinyl chloride in the air or water near hazardous waste sites. However, it would be prudent to consider the possibility of reproductive effects in environmentally exposed populations.

Developmental Effects. Although a statistically significant increase in congenital abnormalities has been observed in members of some communities located near a vinyl chloride processing facility, reports have failed to establish a statistically significant association between developmental toxicity and either parental occupation or proximity to the facility (Edmonds et al. 1978; Infante et al. 1976; Rosenman et al. 1989; Theriault et al. 1983). In contrast, a number of inhalation studies using pregnant animals have shown developmental toxicity consisting of resorptions, delayed ossification, and dilated ureters. These effects occurred when animals were exposed during the first trimester of pregnancy and at high levels of vinyl chloride (500-2,500 ppm) (John et al. 1977, 1981; Ungvary et al. 1978). However, these levels also produced maternal toxicity characterized by increased liver weight, decreased food consumption and weight gain, and increased mortality. Adverse postnatal effects have been observed in rats following *in utero* exposure to low levels of vinyl chloride (Sal'nikova and Kotsovskaya 1980). Therefore, it would be prudent to consider the possibility of developmental effects in environmentally exposed human populations as well. Carcinogenic effects observed after transplacental or postpartum exposure are discussed in this section under "Cancer Effects."

Genotoxic Effects. Vinyl chloride is mutagenic in *S. tphimurium* (Andrews et al. 1976; Bartsch et al. 1975, 1976; de Meester et al. 1980; Elmore et al. 1976; Poncelet et al. 1980; Simmon et al. 1977), but only in strains reverted by base-pair substitution by alkylating agents rather than by frameshift mutations (Bartsch et al. 1976; duPont 1992a, 1992b). Metabolic activation is necessary for any mutagenic activity in this system (Rannug et al. 1974) or for a maximal response (Simmon et al. 1977). In addition, vinyl chloride in the vapor phase is mutagenic but not when it is dissolved in water (Poncelet et al. 1980).

Concentrations of vinyl chloride tested *in vitro* range from 0.275% (Shahin 1976) to 40% (duPont 1992a). Shahin (1976) reported negative results for 0.275% and 0.55% in Succharomyces cerevisiae. In *S. typhimurium,* a doubling of revertants has been reported to occur at about 5% vinyl chloride (Victorin and Stahlberg 1988a). Vinyl chloride was found to be mutagenic in Chinese hamster ovary cells (duPont 1992c). Workers exposed to vinyl chloride have been shown to have increased chromosomal aberrations, micronucleic counts, and sister chromatid exchange frequencies (Anderson et al. 1980; Fucic et al. 1992, 1995; Garaj-Vrhovac et al. 1990; Kucerova et al. 1979; Sinues et al. 1991; Zhao et al. 1994).

There is evidence that in *S. typhimurium* and *Escherichia coli* it is the oxidation of vinyl chloride to the reactive intermediates 2-chloroethylene oxide and 2-chloroacetaldehyde that is responsible for the mutagenicity of vinyl chloride (Jacobsen et al. 1989; McCann et al. 1975; Rannug et al. 1976). Chloroacetaldehyde appears to be less genotoxic in yeast and Chinese hamster V79 cells than 2-chloroethylene oxide (Huberman et al. 1975; Loprieno et al. 1977) and has been shown to inhibit DNA synthesis in avian cells (Kandala et al. 1990). However, 2-chloroacetaldehyde has been shown to react directly with single-stranded DNA, which then caused base changes and subsequent reversion in *E. coli* when the DNA was inserted via phage (Jacobsen et al. 1989). Recent data have also shown 2-chloroacetaldehyde to be mutagenic in human fibroblast cells using shuttle vectors (Matsuda et al. 1995).

Identification of the etheno-derived nucleosides as DNA and RNA adducts following vinyl chloride exposure provides one mechanism for the mutagenicity of this compound (Laib and Bolt 1977). There is evidence that chloroethylene oxide is responsible for the formation of the etheno-DNA adducts, which in turn cause base-pair substitutions (Bar-bin et al 1985a). These findings support the *in vivo* studies (see Section 2.2.1.7) that indicate that 2-chloroethylene oxide is responsible for DNA alkylation as well as preneoplastic foci in the liver. Key *in vivo* genotoxicity studies are presented in Table 2-6, and *in vitro* genotoxicity studies are presented in Table 2-7.

Cancer. A large number of studies have reported a greater than expected incidence of a rare type of cancer, angiosarcoma of the liver, among workers exposed to vinyl chloride (Byren et al. 1976; Creech and Johnson 1974; Fox and Collier 1977; Infante et al. 1976b; Jones et al. 1988; Laplanche et al. 1992; Monson et al. 1975; Pirastu et al. 1990; Rinsky et al. 1988; Simonato et al. 1991; Teta et al. 1990; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989). Other types of

Table 2-6. Genotoxicity of Vinyl Chloride *In Vivo*

Species (test system)	End point	Results	Reference
Mouse	Dominant lethal	–	Purchase et al. 1975
		–	Anderson et al. 1976
Rat	Dominant lethal	–	Short et al. 1977
	Chromosomal aberration	+	Anderson and Richardson 1981
Human lymphocyte	Sister chromatid exchange	–	Hansteen et al. 1978
		+	Kucerova et al. 1979
		+	Sinués et al. 1991
		+	Fucic et al. 1992
		+	Fucic et al. 1995
	Micronuclei	+	Garaj-Vrhovac et al. 1990
		+	Sinués et al. 1991
	Chromosomal aberration	+	Hansteen et al. 1978
		+	Kucerova et al. 1979
		+	Purchase et al. 1978
		+	Ducatman et al. 1975
		+	Anderson et al. 1980
		+	Fucic et al. 1990
		+	Fucic et al. 1995
		+	Funes-Cravioto et al. 1975
		+	Hrivnak et al. 1990
		+	Garaj-Vrhovac et al. 1990
Rat	DNA alkylation	+	Laib et al. 1989
		+	Green and Hathaway 1978
		+	Gwinner et al. 1983
		+	Singer et al. 1987

Table 2-6. Genotoxicity of Vinyl Chloride *In Vivo (continued)*

Species (test system)	End point	Results	Reference
		+	Singer et al. 1987
		+	Bolt et al. 1986
		+	Ciroussel al. 1990
		+	Eberle et al. 1989
Mouse	DNA alkylation	+	Osterman-Golkar et al. 1977
		+	Walles et al. 1988
Rat	DNA adduct	+	Fedtke et al. 1990
		+	Ciroussel et al. 1990
		+	Swenberg et al. 1992

– = negative result; + = positive result; DNA = deoxyribonucleic acid

Table 2-7. Genotoxicity of Vinyl Chloride *In Vitro*

Species (test system)	End point	With activation	Without activation	Reference
Salmonella typhimurium	Reverse mutation	+	–	Rannug et al. 1974
		+	+	Bartsch et al. 1975, 1976
		+	+	Andrews et al. 1976
		+	+	Simmon et al. 1977
		Not tested	–	Elmore et al. 1976
		+	+	Poncelet et al. 1980
		+	+	de Meester et al. 1980
		+	+	Victorin and Stahlberg 1988a
		+	Not tested	McCann et al. 1975
		+	+	Rannug et al. 1976
TA100, TA1535	Base-pair substitution	+	+	duPont 1992a, 1992b
TA98, TA1537, TA1538	Frameshift mutation	–	–	
Escherichia coli		Not applicable	+	Jacobsen et al. 1989
Saccharomyces cerevisiae		Not tested	–	Shahin 1976
Schizosaccharomyces pombe	Forward mutation	+	–	Loprieno et al. 1977
Chinese hamster ovary cells		Not applicable	+	Huberman et al. 1975
		+	–	duPont 1992c
Bacillus subtilis	Rec-repair	Not tested	–	Elmore et al. 1976
Rat liver microsomes	RNA alkylation	Not applicable	+	Laib and Bolt 1977
QT6 (avian cells)	Inhibition of DNA synthesis	Not applicable	+	Kandala et al. 1990

+ = positive result; – = negative result; DNA = deoxyribonucleic acid; RNA = ribonucleic acid

cancer that have shown a statistically significant increase in incidence among vinyl chloride workers, in at least some studies, include cancer of the brain and central nervous system, the lung and respiratory tract, and the lymphatic/hematopoietic system (Belli et al. 1987; Cooper 1981; Infante et al. 1976b; Smulevich et al. 1988; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1991). Because women traditionally have not been employed in PVC-manufacturing positions in North America and Western Europe, virtually all of the information available from occupational studies in these areas is based on the responses of males to vinyl chloride. One study by Smulevich et al. (1988) reporting on Soviet males and females occupationally exposed to vinyl chloride indicates that females may have higher incidences of stomach cancer, leukemias, and lymphomas than males.

An increased incidence of angiosarcoma of the liver has been found after inhalation of vinyl chloride vapor by a variety of animal species (Froment et al. 1994; Maltoni et al. 1981). Although no studies examining the incidence of carcinogenic effects in humans exposed to vinyl chloride by the oral route have been located, vinyl chloride incorporated into the diet of rats has been demonstrated to cause an increased incidence of hepatic angiosarcoma (Maltoni et al. 1981). Based on these and other findings, the National Toxicology Program of the Department of Health and Human Services has determined vinyl chloride to be a carcinogen (DHHS 1994). In addition, IARC has concluded that sufficient evidence for carcinogenicity in humans and animals exists and has placed vinyl chloride in carcinogenicity category 1, i.e., carcinogenic to humans (IARC 1987). EPA also has concluded that sufficient evidence of carcinogenicity exists in humans and animals and has classified vinyl chloride according to its classification scheme as a Group A carcinogen, i.e., a human carcinogen (EPA 1994c). Because the epidemiological evidence does not provide sufficient exposure and incidence data to quantify risk based solely on human data, EPA cancer potency factors for inhalation and oral exposure have been calculated based on animal studies. An upper-bound q_i^* of 2.95×10^{-1} $(mg/kg/day)^{-1}$ for inhalation exposure was estimated by EPA (1985c) based on the incidence of hepatic angiosarcoma observed in rats in the inhalation study by Maltoni et al. (1981). An upper-bound q_l^* for oral exposure was estimated by EPA (1985b) to be 2.3 $(mg/kg/day)^{-1}$ based on the combined incidence of liver and lung tumors in rats in the study by Feron et al. (1981). Doses associated with excess cancer risks of 10^{-4}, 10^{-5}, and 10^{-6} by the inhalation and oral routes are plotted in Figures 2-l and 2-2, respectively. The above risks were not calculated using PBPK modeling. Further discussion of the risks associated with vinyl chloride exposure, which are based on PBPK models, can be found in Section 2.3.5.

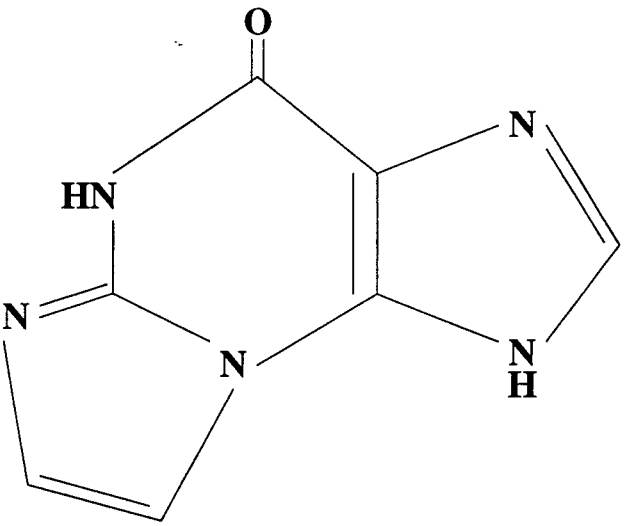
There are ample data on the genotoxicity of vinyl chloride in both humans and animals. Information on the mechanisms by which this compound may exert its carcinogenic effects have been elucidated from both *in vitro* and *in vivo* studies. Vinyl chloride is metabolized to 2-chloroethylene oxide, which interacts directly with DNA and RNA, producing alkylation products such as 3,N^4-etheno-2'-deoxycytidine, l,N^6-etheno-2'-deosy-adenosine, and 7-N-(2'-oxoethyl)-guanine (Fedtke et al. 1990; Swenberg et al. 1992). This alkylation results in highly efficient base-pair substitution. PBPK models were not used to estimate the amount of chloroethylene oxide formed in the tissues, and no risk estimates were presented in these studies. It appears that the oxide is the ultimate genotoxic intermediate of vinyl chloride, which is consistent with data on the carcinogenicity of the oxirane derivatives of vinyl chloride. Figure 2-5 shows the DNA adducts 7-(2'-oxoethyl)guanine (OEG) and N^2,3-ethenoguanine (EG) (Fedtke et al. 1990).

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

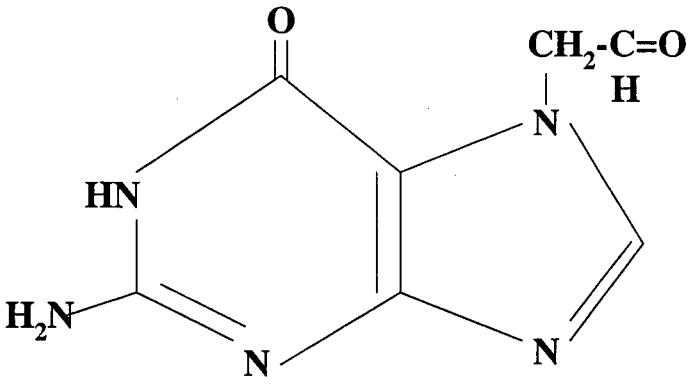
Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NASLNRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NASLNRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to vinyl chloride are discussed in Section 2.6.1.

FIGURE 2-5. The Vinyl Chloride-Induced DNA Adducts 7-(2'-oxoethyl)guanine (OEG) and N^2,3-ethenoguanine (EG)*



EG



OEG

*Fedtke et al. 1990

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NASLNRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by vinyl chloride are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Vinyl Chloride

Exposure to vinyl chloride may be monitored to some extent by the identification and quantitation of a number of parameters. For example, following acute exposure to moderate-to-high levels, vinyl chloride can be measured in expired air. The expiration of vinyl chloride follows first-order kinetics; therefore, this parameter may be directly correlated with exposure levels (Baretta et al. 1969). This measure may provide the most direct evidence of vinyl chloride exposure. However, measurement of exposure by this technique is limited by the rapidity of excretion of vinyl chloride in expired air. The half-life of vinyl chloride in expired air has been determined to be between 20 and 30 minutes following an inhalation exposure and to be approximately 60 minutes following an oral exposure (Watanabe and Gehring 1976; Watanabe et al. 1976b, 1978a, 197Sb). Thus, testing must be initiated as soon as possible following termination of exposure. Furthermore, measurement of vinyl chloride in expired air has limited utility for low-level exposures (<50 ppm) because of competition with absorption and rapid metabolic processes (Baretta et al. 1969). In addition, it provides no information on the duration of exposure.

Thiodiglycolic acid is a major metabolite of vinyl chloride that is excreted in the urine. Measurement of thiodiglycolic acid in urine has been used to monitor workers occupationally exposed to vinyl

chloride (Muller et al. 1979). However, although this metabolite is used to estimate levels of exposure, the amount of thiodiglycolic acid in the urine varies according to individual metabolic idiosyncracies. Also, metabolism of vinyl chloride to thiodiglycolic acid is a saturable process. Therefore, when exposure exceeds a certain level, the excretion of vinyl chloride as thiodiglycolic acid will plateau (Watanabe and Gehring 1976). Furthermore, the rate of metabolism of vinyl chloride to thiodiglycolic acid may be influenced by the presence of liver disease, ethanol, or certain other substances such as barbiturates (Hefner et al. 1975b) (also see Section 2.7). Similar to the measurement of vinyl chloride in expired air, the measurement of thiodiglycolic acid must take place shortly after exposure because of the rapidity of its excretion. The half-life for excretion of thiodiglycolic acid following an acute exposure is between 4 and 5 hours (Watanabe and Gehring 1976; Watanabe et al. 1978a, 1978b). Finally, excretion of thiodiglycolic acid is not unique to exposure to vinyl chloride. For example, thiodiglycolic acid may be excreted in the urine as the result of exposure to vinylidene chloride, ethylene oxide, or 2,2-dichloroethylether (Norpoth et al. 1986; Pettit 1986). Also, infants delivered prematurely have been found to have high levels of urinary thiodiglycolic acid. A correlation was observed between the thiodiglycolic acid levels and the number of weeks that.the infant was born prematurely. The origin of this thiodiglycolic acid is unknown but is not believed to be associated with vinyl chloride exposure (Pettit 1986).

The intermediary metabolites, 2-chloroethylene oxide and 2-chloroacetaldehyde, bind to macromolecules in the body. 2-Chloroethylene oxide is believed to bind primarily to DNA and RNA, whereas 2-chloroacetaldehyde binds primarily to proteins (Bolt 1986; Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). Two of the DNA adducts that are formed are 1 ,N6-etheno-adenosine and 3,V-ethenocytidine. Monoclonal antibodies for these DNA adducts have been isolated and used in enzyme-linked immunosorbent assay (ELISA) to quantify these ethenoderivatives in biological samples (Eberle et al. 1989; Young and Santella 1988). Measurement of DNA adducts may be useful in estimating vinyl chloride exposure. However, this technique is of limited value for quantifying levels of exposure because formation of these products will be influenced by variability in vinyl chloride metabolism. Also, their persistence in tissues will be influenced by the rate of DNA metabolism and repair. Furthermore, the DNA adducts, for which monoclonal antibodies have been isolated, are formed as a result of exposure to vinyl bromide, ethyl carbamate, acrylonitrile, 2-cyanoethylene, and 1,Zdichloroethane (Bolt et al. 1986; Svensson and Osterman-Golkar 1986). See Section 2.3 for additional information on the kinetics of vinyl chloride.

The micronucleus assay, performed using peripheral lymphocytes of 32 vinyl chloride workers, was used to indicate the time elapsed since the last vinyl chloride exposure occurred (Fucic et al. 1994). The study showed a decrease in the frequency of micronuclei in proportion to length of the interval after the last vinyl chloride exposure. For the group with 10 years of employment, the percentage of micronuclei decreased from 12.82 when exposure occurred on the day of blood sampling to 3.16 when the last exposure occurred 90 days before blood sampling (Fucic et al. 1994). Similar changes were noted when the mean duration of employment was 5 years. However, this use of the micronucleus assay must take into account the total duration of exposure.

Exposure to vinyl chloride may also be estimated to some extent by the presence of certain symptoms known to be closely associated with vinyl chloride exposure. The exposure may have occurred even if the symptoms were not found upon examination, but their presence could be indicative of exposure. For example, a syndrome known as vinyl chloride disease has been identified in workers occupationally exposed to vinyl chloride. This syndrome includes Raynaud's phenomenon, acroosteolysis of the distal phalanges of the fingers, and scleroderma-like changes in the hands and forearms (also see Section 2.2). Although this syndrome resembles systemic sclerosis, a differential diagnosis may be made based on the absence of antinuclear antibodies from the blood of those afflicted with vinyl chloride disease (Black et al. 1983, 1986). The occurrence of vinyl chloride disease in highly exposed worker populations is about 3%, and susceptibility appears to be genetically related (Black et al. 1983, 1986). Symptoms of vinyl chloride disease are unlikely to occur in hazardous waste site conditions because of predicted low levels of exposure. Absence of these symptoms would not eliminate the possibility of exposure, but their presence may be a good indicator of exposure.

Angiosarcoma of the liver has been identified in workers occupationally exposed to vinyl chloride. This type of tumor is extremely rare in the general population (Heath et al. 1975); therefore, its diagnosis may indicate vinyl chloride exposure. However, other causes of angiosarcoma such as exposure to arsenicals and Thorotrast (thorium dioxide; formerly used in arteriography) should be considered as possible causative factors if present before correlating hepatic angiosarcoma with vinyl chloride exposure (Gedigke et al. 1975; Marsteller et al. 1975). Their elimination may depend upon such factors as the magnitude of the vinyl chloride exposure and the frequency of the other causes of angiosarcoma in the population.

2.6.2 Biomarkers Used to Characterize Effects Caused by Vinyl Chloride

The realization that angiosarcoma of the liver is associated with vinyl chloride exposure prompted several investigators to try to identify assays that could be used to monitor those individuals considered to be at risk. Standard serum assays designed to detect the presence of hepatic enzymes in the blood were found to be of limited value in monitoring the progression of vinyl chloride-induced hepatic changes (Berk et al. 1975; Liss et al. 1985; Vihko et al. 1984). This may be because of the relatively slight hepatic damage produced by vinyl chloride and the late development of necrotic areas in the disease process (Popper et al. 1981). In contrast, studies indicate that clearance type assays, which measure liver function, are more sensitive indicators of the hepatic damage resulting from vinyl chloride exposure. Two such assays are the indocyanine clearance test and measurement of serum bile acid levels (Berk et al. 1975; Liss et al. 1985; Vihko et al. 1984).

Liver biopsy may provide the most accurate identification of vinyl chloride-associated liver damage (Liss et al. 1985). This is because of the characteristic pattern of hepatic histopathology associated with vinyl chloride-induced damage (Popper et al. 1981). However, liver biopsy is an invasive procedure with attendant risks and, therefore, may not be justified.

Individual exposure to vinyl chloride has been linked to angiosarcoma and benign angiomatous lesions based on the monitoring of serum found to be positive for the presence of the mutant protein Asp 13 c-Ki-*ras* p21, which was not present in control individuals (DeVivo et al. 1994). Additionally, this protein was found in the serum of 49% of exposed workers who had no apparent liver lesions. It may be possible to utilize the presence of this mutant protein for the early detection of angiosarcoma of the liver.

Use of enzyme-linked immunoassay (EIA) to detect anti-p53 antibodies in serum of individuals exposed to vinyl chloride may provide an early method of screening for angiosarcoma of the liver (Trivers et al. 1995). Detection of serum anti-p53 antibodies has occurred in some, but not all, individuals exposed to vinyl chloride who later developed angiosarcoma of the liver (Trivers et al. 1995). However, not all individuals who developed angiosarcoma of the liver tested positive for anti-p53 antibodies. Also, anti-p53 antibodies are not specific to angiosarcoma of the liver but can be detected in the sera of patients with other types of cancers such as leukemia; childhood lymphoma; breast, lung, and colon cancer; and hepatocellular carcinoma.

The symptoms and signs associated with vinyl chloride disease (Raynaud's phenomenon, sclerodermalike skin changes, and acroosteolysis) are similar to those observed in systemic sclerosis. Vinyl chloride disease may be differentiated from systemic sclerosis by the absence of antinuclear antibodies in the blood and association of vinyl chloride disease with vinyl chloride exposure (Black et al. 1983, 1986). Raynaud's phenomenon is an early symptom of vinyl chloride disease. However, cyanosis and blanching of fingers with exposure to cold may be the result of a number of other conditions such as connective tissue disorders, mechanical arterial obstruction, hyperviscosity of the blood, or exposure to drugs, chemicals, or vibrating tools (Freudiger et al. 1988). Thus, other potential causes must be eliminated before this syndrome can be used to identify vinyl chloride disease. The symptoms associated with vinyl chloride disease have been attributed to vinyl chloride-induced changes in the microvasculature (Grainger et al. 1980). Capillary abnormalities in the hands may be detected using wide-field capillary microscopy and have been proposed to represent an early manifestation of the effects of vinyl chloride (Maricq et al. 1976). Also, immunofluorescent examination of biopsy material from the skin may be used to identify circulating immune complexes and their deposition on the vascular endothelium (Ward 1976).

Chromosomal aberrations found in lymphocytes may be indicative of the genotoxic effects of vinyl chloride (Anderson et al. 1980; Ducatman et al. 1975; Fucic et al. 1990, 1992; Funes-Cravioto et al. 1975; Garaj-Vrhovac et al. 1990; Hansteen et al. 1978; Hrivnak et al. 1990; Kucerova et aL 1979; Purchase et al. 1978; Sinues et al. 1991). However, any of a number of genotoxic substances can cause chromosomal aberrations. Also, de Jong et al. (1988) have found that variability in the control population may obscure the observation of low-level chromosomal aberrations in persons exposed to low levels of vinyl chloride. G-banding analysis appeared to provide a more sensitive indication of chromosomal alteration than sister chromatid exchanges (Zhao et al. 1994). The DNA adducts produced by the reactive intermediary metabolites of vinyl chloride, including l,N^6-ethenoadenosine and 3,N^4-ethenocytidine, may be more specific indicators of vinyl chloride's genotoxic potential.

2.7 INTERACTIONS WITH OTHER SUBSTANCES

A number of studies have been performed that examine the effect of agents intended to alter the metabolism of vinyl chloride on its toxicity. For example, the effects of phenobarbital pretreatment on vinyl chloride-induced hepatotoxicity have been examined by Jaeger et al. (1974, 1977), Jedrychowski et al. (1985), and Reynolds et al. (1975a, f975b). Pretreatment of rats with phenobarbital for 7 days

prior to a 4-hour vinyl chloride exposure caused an increase in microsomal cytochrome P-450 activity (Reynolds et al. 1975b) and enhanced hepatotoxicity (Jaeger et al. 1974, 1977; Jedrychowski et al. 1985; Reynolds et al. 1975a, 1975b). In these studies, in the absence of the phenobarbital pretreatment, a single exposure to approximately 50,000 ppm had no detectable adverse effect on the livers of exposed rats. However, following phenobarbital pretreatment, 50,000 ppm of vinyl chloride produced increased serum activity of hepatic enzymes (Jaeger et al. 1977; Jedrychowski et al. 1985), areas of hepatic necrosis (Reynolds et al. 1975a), or both (Jaeger et al. 1974; Reynolds et al. 1975b).

Another agent known to increase MFO activity, Aroclor 1254, was also tested for its ability to enhance vinyl chloride-induced hepatotoxicity (Conolly and Jaeger 1979; Conolly et al. 1978; Jaeger et al. 1977; Reynolds et al. 1975b). Pretreatment of rats with Aroclor 1254 for several days prior to exposure to vinyl chloride resulted in an increase in serum activity of hepatic enzymes (Conolly and Jaeger 1979; Conolly et al. 1978; Jaeger et al. 1977; Reynolds et al. 1975b) and areas of hepatic necrosis (Conolly et al. 1978; Reynolds et al. 1975b).

Additional support for a role for MFO in the enhanced toxicity of vinyl chloride was obtained using SKF525A, an MFO inhibitor. If SKF525A was administered following phenobarbital pretreatment and before vinyl chloride exposure, it blocked the ability of phenobarbital pretreatment to enhance vinyl chloride-induced hepatotoxicity (Jaeger et al. 1977).

The role of glutathione conjugation in vinyl chloride-induced toxicity was also examined (Conolly and Jaeger 1979; Jaeger et al. 1977). The investigators hypothesized that depletion of glutathione might enhance the toxicity of vinyl chloride by preventing the excretion of toxic intermediary metabolites. However, diethylmaleate, an agent known to deplete hepatic glutathione levels, had no effect on the toxicity produced by vinyl chloride following pretreatment with either phenobarbital (Jaeger et al. 1977) or Aroclor 1254 (Conolly and Jaeger 1979). Trichloropropene oxide (TCPO), another agent known to deplete hepatic glutathione, caused enhancement of the hepatic toxicity produced by Aroclor 1254 pretreatment and vinyl chloride exposure but only when the animals had been fasted prior to vinyl chloride exposure (Conolly and Jaeger 1979). The study authors hypothesized that the enhancement of vinyl chloride toxicity was a result of the ability of TCPO to inhibit epoxide hydrase rather than its ability to deplete glutathione levels. The lack of the effect of glutathione depletion indicates that the glutathione pathway is not very important at normal levels of exposure.

Although the depletion of cellular glutathione levels did not appear to enhance vinyl chloride toxicity, treatment with cysteine, the rate-limiting precursor in hepatic glutathione synthesis, increased hepatic glutathione levels and provided partial protection against the toxic effects produced by Aroclor 1254 and vinyl chloride (Conolly and Jaeger 1979).

The effects of the interaction of ethanol with vinyl chloride on development were tested by John et al. (1977). In this study, animals were exposed to vinyl chloride in the presence and absence of 15% ethanol in the drinking water during pregnancy. Ethanol caused a decrease in maternal food consumption and maternal weight gain in mice, rats, and rabbits and enhanced incidence of skeletal abnormalities in mice, and to a lesser extent, in rats. Interpretation of these results is clouded by the absence of an ethanol-exposed control group and the current recognition of the adverse effects of ethanol on pregnancy outcome.

In the experiment by Radike et al. (1981), ethanol-consuming rats exposed to vinyl chloride for a year had an enhanced incidence of hepatic angiosarcomas, hepatomas, and lymphosarcomas, earlier onset of the tumors, and an enhanced death rate. The incidence of vinyl chloride-induced angiosarcomas was potentiated by ethanol, whereas the increased incidences of hepatoma and lymphosarcomas by ethanol were additive in nature.

The effects of smoking on chromosomal aberrations in vinyl chloride-exposed workers was examined by Hrivnak et al. (1990) who found no effect of smoking in 43 workers exposed for an average of 11.2 years to levels of vinyl chloride ranging from 0.8 to 16 ppm. Most cytogenetic studies of the effects of smoking in humans have reported no effect on chromosomal aberrations, although the sister chromatid exchange frequency is usually elevated.

A study that examined the interaction between vinyl chloride and trichloroethylene using both inhalation exposures of rats and pharmacokinetic modeling found that trichloroethylene exposure inhibited vinyl chloride in a competitive manner (Barton et al. 1995). This interaction was observed only at high concentrations (both chemicals greater than 10 ppm), and the study authors concluded that the interaction is not likely to be important for environmental exposures.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to vinyl chloride than will most persons exposed to the same level of vinyl chloride in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of vinyl chloride, or compromised function of organs affected by vinyl chloride. Populations who are at greater risk due to their unusually high exposure to vinyl chloride are discussed in Section 5.6, Populations With Potentially High Exposures.

Data suggest that the following subsets of the human population may be unusually susceptible to the toxic effects of vinyl chloride: fetuses; infants; young children; people with liver disease, irregular heart rhythms, impaired peripheral circulation, or systemic sclerosis; people with exposure to organochlorine pesticides; and those consuming ethanol or barbiturates or taking Antabuse for alcoholism. Also, persons who possess the HLA-DRS, HLA-DR3, and B8 alleles may be at increasec risk.

Vinyl chloride can cross the placenta and enter the blood of the fetus (Ungvary et al. 1978). Studies by Drew et al. (1983), John et al. (1977, 1981), and Maltoni et al. (1981) have shown that animals exposed by inhalation prior to adolescence or during pregnancy may have a greater death rate and increased likelihood of developing cancer than adult animals exposed for similar periods. This may relate to the length of the induction period of hepatic angiosarcoma rather than to an increased susceptibility of the young, per se. It is also possible that there are explanations for these findings. Cogliano and Parker (1992) suggested that in the multistage model of carcinogenesis, carcinogens that induce an initial transition early in the life of an animal would be more effective since there would be a longer period of time remaining in the lifespan for completion of the remaining transitions. Their empirical model of the effect of age at exposure on the development of cancer suggests that there is an age-sensitive period of exposure to vinyl chloride.

Vinyl chloride is metabolized in the liver in a multistep process. The intermediary metabolites of vinyl chloride, 2-chloroethylene oxide and 2-chloroacetaldehyde, have been suggested to be responsible for some of the adverse effects produced by vinyl chloride. Thus, activation of the enzyme system responsible for production of these toxic metabolites would be expected to increase the

toxicity of vinyl chloride exposures. 2-Chloroethylene oxide is formed by action of the mixed function oxidase system associated with cytochrome P-450. The barbiturate, phenobarbital, and the pesticide extender, Aroclor 1254, increased MFO activity and have been shown to greatly increase the hepatotoxicity of vinyl chloride (Conolly and Jaeger 1979; Conolly et al. 1978; Jaeger et al. 1974, 1977; Jedrychowski et al. 1985; Reynolds et al. 1975a, 1975b). Thus, persons taking barbiturates or who might be exposed to organochlorine pesticides that are known to induce microsomal enzymes (such as Aroclor 1254) would be expected to be at increased risk for developing vinyl chloride-induced hepatotoxicity.

Radike et al. (1981) demonstrated that ethanol-consuming rats exposed to vinyl chloride had an increased incidence of cancer and an earlier death rate than animals exposed to vinyl chloride in the absence of ethanol.

Some persons consume the agent, Antabuse, to curb the desire for alcohol. In its role as a therapeutic agent, Antabuse blocks aldehyde dehydrogenase and causes a build-up of acetaldehyde, which is emetic, in the body when alcohol is consumed. If persons taking Antabuse are exposed to vinyl chloride, the alternative metabolic pathway for vinyl chloride metabolism will be blocked, causing more vinyl chloride to be metabolized to the toxic metabolite, 2-chloroethylene oxide. Thus, these persons may be at increased risk for hepatotoxicity, cancer, and early death.

Very high levels of vinyl chloride have been demonstrated to cause cardiac arrhythmias in dogs (Carr et al. 1949; Oster et al. 1947). Persons with a propensity to develop cardiac arrhythmias because of heart disease or damage may be at an increased risk of having heart beat irregularities when exposed to high concentrations of vinyl chloride.

Vinyl chloride has been shown to cause decreased circulation in the hands and fingers of some persons. Persons with impaired circulation due to some other cause such as connective tissue disorders, systemic sclerosis, hyperviscosity of the blood, or use of vibrating tools, may experience more severe impairment of the circulation.

Work by Black et al. (1983, 1986) has shown that persons with the HLA allele HLA-DR5 may have an increased likelihood of developing vinyl chloride disease, and those with the alleles HLA-DR3 and B8 may have an increased severity of the disease.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to vinyl chloride. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to vinyl chloride. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to vinyl chloride: Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Ulin 1992.

2.9.1 Reducing Peak Absorption Following Exposure

Limited information from humans and results from animal studies indicate that vinyl chloride is rapidly and virtually completely absorbed following inhalation and oral exposure, but animal studies suggest that dermal absorption of vinyl chloride vapor is not likely to be significant (see Section 2.3.1). Efforts to reduce absorption following acute exposure to vinyl chloride should focus on removing the individual from the site of exposure and decontaminating exposed areas of the body. Vinyl chloride gas is relatively dense and accumulates at ground level. Therefore, the subject should be moved from low-lying areas. Contaminated skin may be washed with soap and water; however, this will most likely not prevent tissue damage caused by frostbite from the cooling caused by the rapid evaporation of vinyl chloride from the skin. It is suggested that eyes exposed to vinyl chloride be copiously irrigated with water or normal saline (Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Ulin 1992). Because of its volatility, it is unlikely that vinyl chloride would be ingested unless it had been dissolved in a solvent. If such ingestion of vinyl chloride occurs, it is suggested that water or milk be administered for dilution if the patient can swallow, has a good gag reflex, and is not drooling (Bronstein and Currance 1988; Stutz and Ulin 1992). In addition, gastric lavage and administration of activated charcoal have been suggested as a means to reduce absorption of vinyl chloride. Induction of emesis is contraindicated (Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Ulin 1992).

2.9.2 Reducing Body Burden

Because of its rapid metabolism and excretion, vinyl chloride does not tend to accumulate in the body. As discussed in Section 2.3.3, the metabolism of vinyl chloride is a dose-dependent, saturable process. Vinyl chloride is oxidized primarily by the microsomal MFO system (cytochrome P-450) to a reactive epoxide intermediate (Zchloroethylene oxide), which can rearrange to 2-chloroacetaldehyde or conjugate with glutathione to form S-formylmethyl glutathione. At exposure concentrations below about 1,000 ppm in air, very little vinyl chloride is excreted unchanged in the exhaled air. However, when metabolic saturation occurs at high exposure concentrations (approximately 1,000 ppm following inhalation exposure in rats [Watanabe and Gehring 1976; Watanabe et al. 1976b] and approximately 20 mg/kg following oral administration to rats [Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a]), vinyl chloride is excreted unchanged in expired air. Therefore, a possible means to enhance the elimination of vinyl chloride without allowing its biotransformation to toxic intermediates is to saturate this oxidative pathway by administration of substances known to be metabolized via this route. Saturation of the P-450 system may occur with drugs such as phenytoin or dicumerol (Goodman and Gilman 1980). However, the effectiveness of these agents in blocking the P-450 metabolism of vinyl chloride has not been tested, and it is unclear whether toxic doses would be necessary to overcome the relative affinities of the enzymes for vinyl chloride versus these agents. In addition, the potential toxicity of any side products of these substances would need to be considered in any protocol. Several agents induce activity of the microsomal enzymes and could potentially increase the toxicity of vinyl chloride. Administration of such substances would be contraindicated.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Following acute, high-level exposure, vinyl chloride behaves as an anesthetic and causes central nervous system and respiratory depression (see Sections 2.2.1.4 and 2.2.2.4). Therefore, basic life support measures, such as supplemental oxygen and cardiopulmonary resuscitation, are suggested in such instances (Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Ulin 1992). In addition, like other halogenated hydrocarbons, vinyl chloride may sensitize the heart to the effects of circulating catecholamines. Therefore, the patient’s cardiac rhythm should be monitored, and the use of isoproterenol, epinephrine, or other sympathomimetic drugs should be avoided (Haddad and Winchester 1990).

Vinyl chloride is a known human and animal carcinogen; long-term exposure to this compound is associated with an increased incidence of hepatic angiosarcomas (see Section 2.2.1.8). Vinyl chloride is also hepatotoxic. The mechanism by which vinyl chloride induces its carcinogenic and toxic effect on the liver has been well studied. It is currently believed that these effects are mediated by a reactive epoxide intermediate of vinyl chloride, 2-chloroethylene oxide, which interacts directly with DNA and RNA producing alkylation products such as 3#-ethenocytidine, l,N6-ethenoadenosine, and 7-N-(2-oxoethyl)-guanosine. This alkylation results in highly efficient base-pair substitution, leading to neoplastic transformation (see Section 2.4). As discussed above, this epoxide intermediate is formed when vinyl chloride is oxidized by the P-450 isoenzymes. Interference with this metabolic pathway, therefore, could reduce the toxic and carcinogenic effects of vinyl chloride by reducing the amount of epoxide produced. A number of drugs, such a cobaltous chloride, SKF-535-A, and 6-nitro-1,2,3-benzothioadiazole, have been reported to inhibit P-450 enzymes. Pretreatment with 6-nitro-1,2,3-benzothioadiazole completely blocked the metabolism of vinyl chloride in rats exposed to 0.45 ppm in a closed system for 5 hours (Bolt et al. 1977). P-450 metabolism also results in products that can be more readily eliminated than can the parent compound. Hence, any side products of the drugs and their potential to increase the biological half-life of vinyl chloride would also need to be considered in any protocol. In fact, a study by Buchter et al. (1977) showed that substantial unmetabolized vinyl chloride accumulated in fatty tissue when 6-nitro-1,2,3-benzothioadiazole was used to block P-450 metabolism. The study did not examine the fate of vinyl chloride in fatty tissue after P-450 metabolism was reactivated, but it is likely that vinyl chloride would leave the fat slowly and be metabolized. Thus, while P-450 metabolism would probably reduce the generation of toxic metabolites in the short term, it is unclear whether the generation of toxic metabolites could be completely avoided. Further research to determine which isozymes are involved in the metabolism to the reactive intermediates, as well as which isozymes are involved in enhancing the elimination of vinyl chloride, could lead to the development of strategies to selectively inhibit specific isozymes and thus reduce the toxic effects of vinyl chloride.

Because vinyl chloride is detoxified by conjugation with glutathione and/or cysteine (see discussion above and Section 2.3.3), ensuring sufficient glutathione stores in the body (e.g., by treatment with N-acetyl cysteine) may reduce the possibility of toxic effects following acute exposure to vinyl chloride.

2.HEALTH EFFECTS

Vinyl chloride disease has been reported in a small percentage of workers exposed to this compound. One of the symptoms of this condition is Raynaud's syndrome (blanching, numbness, and discomfort of the fingers upon exposure to cold). Studies of these individuals demonstrated that vinyl chloride may cause blockage of the blood vessels supplying the hand, hypervascularity, and a thickening of the blood vessel walls (Harris and Adams 1967; Preston et al. 1976; Veltman et al. 1975; Walker 1976). Several investigators have suggested that the mechanism for vinyl chloride disease may be an autoimmune response similar to systemic sclerosis. Grainger et al. (1980) and Ward (1976) proposed that a reactive vinyl chloride intermediate metabolite, such as 2-chloroethylene oxide or 2-chloroacetaldehyde, binds to a protein such as IgG. The altered protein initiates an immune response, with deposition of immune products along the vascular endothelium. Cold temperatures could cause the precipitation of these immune complexes resulting in blockage of the blood vessels. Another characteristic of vinyl chloride disease is acroosteolysis, in which the terminal phalanges of the fingers are resorbed. This condition has been noted predominantly in workers who first had Raynaud's syndrome (Dinman et al. 1971; Freudiger et al. 1988; Harris and Adams 1967; Magnavita et al. 1986; Markowitz et al. 1972; Preston et al. 1976; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967). The resorptive bone changes may be due to activation of osteoclasts secondary to vascular insufficiency in the finger tips, but this remains to be demonstrated conclusively. Other manifestations of vinyl chloride disease include joint and muscPe pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes. Increased levels of circulating immune complexes and immunoglobulins have been observed in vinyl chloride workers, suggesting a stimulatory effect of vinyl chloride on the immune system (Bogdanikowa and Zawilska 1984). A correlation between the severity of the symptoms of vinyl chloride disease and the magnitude of the immune response was observed (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976). Research on the genetic characteristics of workers with this disease has demonstrated that the susceptibility to vinyl chloride disease was increased in the presence of the HLA-DR5 allele or a gene in linkage disequilibrium with it, and progression of the disease to its more severe forms was favored by HLADR3 and B8 (Black et al. 1983, 1986). If vinyl chloride disease is mediated by an immune mechanism in individuals with a genetic predisposition, then the effects of this disease may be mitigated by administration of drugs used to treat other similar autoimmune diseases (e.g., azathioprine, cyclophosphamide, and prednisone). However, the toxicity associated with the use of these drugs must also be considered.

2.10 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of vinyl chloride is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of vinyl chloride.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.10.1 Existing Information on Health Effects of Vinyl Chloride

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to vinyl chloride are summarized in Figure 2-6. The purpose of this figure is to illustrate the existing information concerning the health effects of vinyl chloride. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specijic Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Virtually all of the literature regarding health effects in humans comes from studies of workers exposed to vinyl chloride during the production of PVC. Case reports and cohort studies describe some acute health effects and a wide range of long-term health effects. The predominant mode of exposure in these studies is via inhalation. These studies are limited by the lack of reliable data on individual exposure levels. No studies were found regarding the health effects of oral exposure. One

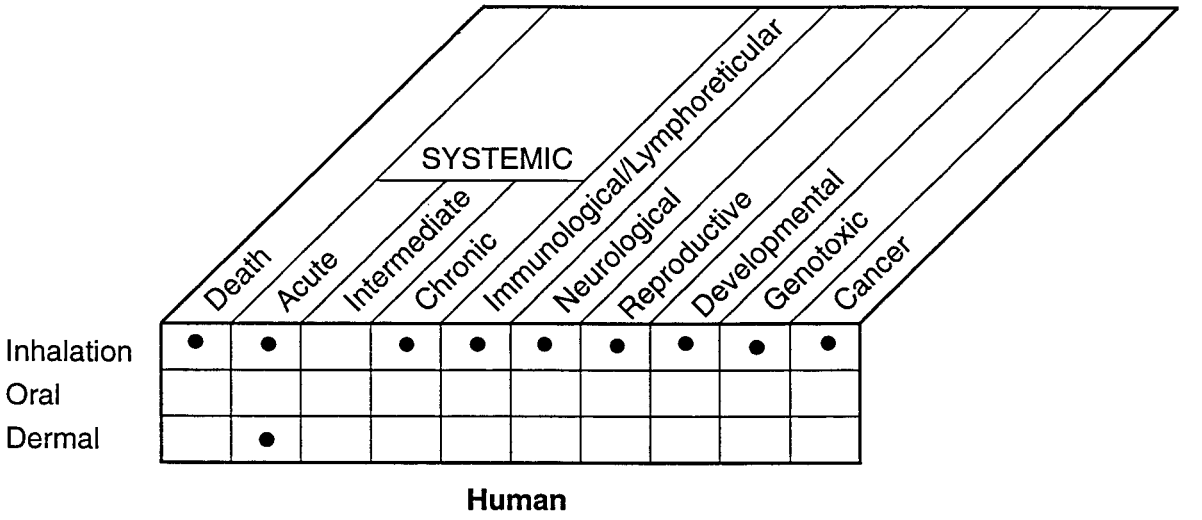
case report examined the effects of dermal exposure to liquid vinyl chloride, but exposure by this route is not expected to contribute significantly to producing adverse health effects because of the limited absorption of vinyl chloride through the skin.

A large number of studies examining the health effects of inhaled vinyl chloride in animals were reviewed. As can be seen in Figure 2-6,. no information is available on the acute systemic, immunologic, neurologic, reproductive, developmental, or genotoxic effects of exposure of animals by the oral route. No information is available regarding the health effects of exposure by the dermal route, but toxicokinetic studies indicate that this route is not an important means of exposure.

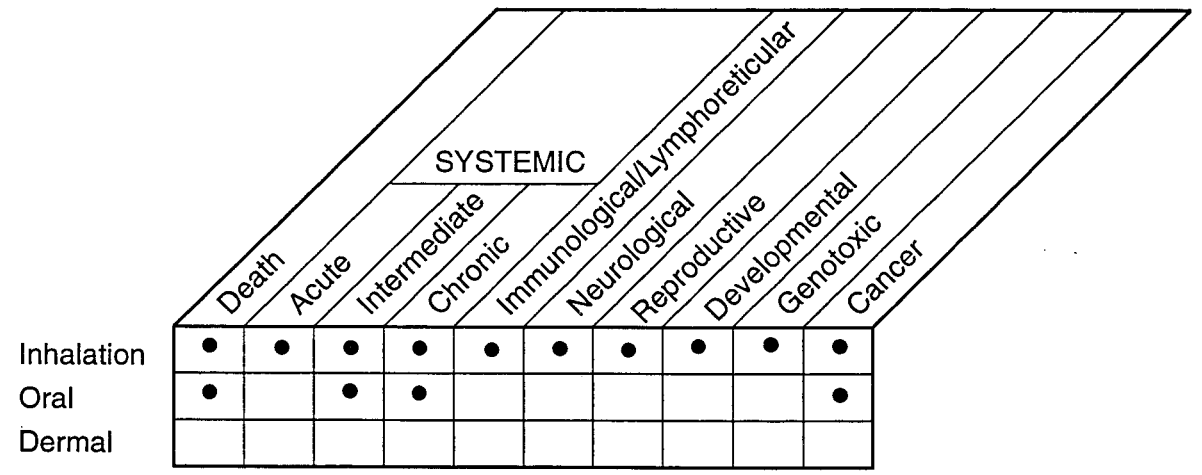
2.10.2 Identification of Data Needs

Acute-Duration Exposure. Populations in areas that contain hazardous waste sites may be exposed to vinyl chloride for brief periods. Exposure most likely would occur by inhalation, but relatively brief oral and dermal exposures are also possible. There are acute inhalation exposure data in humans and animals that indicate that the central nervous system is a major target organ of vinyl chloride toxicity. Symptoms of central nervous system depression ranging from dizziness and drowsiness to loss of consciousness have been observed in humans and animals as a result of brief exposure to very high levels of vinyl chloride (Hehir et al. 1981; Jaeger et al. 1974; Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930). A threshold for central nervous system effects appears to be approximately 8,000 ppm (Lester et al. 1963). Extremely high concentrations of vinyl chloride produce respiratory irritation and death in humans and animals by the inhalation route (Danziger 1960; Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930). Based on studies in animals, the threshold for these effects appears to be in the range of 100,00-400,000 ppm (Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930). However, increased death was noted in pregnant mice at 500 ppm (John et al. 1977, 1981). Extremely high concentrations of vinyl chloride produced cardiac arrhythmias in dogs exposed by the inhalation route (Carr et al. 1949; Oster et al. 1947). Although no threshold was reported for these effects, no further acute inhalation studies examining the incidence of cardiac irregularities are required. Pharmacokinetic data indicate that similar end points might be expected if sufficiently high doses could be consumed by the oral route. However, the solubility characteristics of vinyl chloride in aqueous media (l,100-2,763 mg/L at 25°C) (Cowfer and Magistro 1983; EPA 1985b) indicate that achieving concentrations of vinyl chloride in excess of 5,000 ppm may be extremely difficult. Animal studies indicate that an adverse effect on the fetus is the most sensitive

FIGURE 2-6. Existing Information on Health Effects of Vinyl Chloride



Human



Animal

● Existing Studies

end point observed following brief inhalation exposures to vinyl chloride (John et al. 1977, 1981; Ungvary et al. 1978). Concentrations as low as 500 ppm were observed to cause adverse effects on developing fetuses (John et al. 1977, 1981). The NOAEL (50 ppm) in this study was used to derive an acute-duration inhalation MRL. Animal studies examining the developmental, neurological, and systemic effects of the highest doses achievable in drinking water would be helpful for determining whether any effects would occur when vinyl chloride-contaminated groundwater or food products are consumed. One report described severe frostbite with second degree bums on the hands of a man resulting from the rapid evaporation of spilled liquid vinyl chloride (Harris 1953). A toxicokinetic study using two monkeys indicates that absorption of vinyl chloride vapor by the dermal route is exceedingly small (Hefner et al. 1975a); thus, studies examining the effects of acute-duration dermal exposure do not seem warranted. However, if further toxicokinetics studies contradict these findings, acute-duration dermal exposure studies in animals may be needed.

A report was located regarding hepatic and respiratory effects observed 18 months following a single l-hour inhalation exposure to vinyl chloride (Hehir et al. 1981). However, limitations in the study diminished its reliability. Because of the implications of chronic effects from acute exposure, confirmation of these results in another study would be valuable.

Intermediate-Duration Exposure. No studies in humans specifically address intermediate-duration effects by any route. Most epidemiological studies of occupationally exposed persons have concentrated on persons who have been employed over several years. A study with reliable quantification of exposure levels that examined the effects experienced by vinyl chloride workers in their first year of exposure would be helpful for predicting the effects that might be observed in populations exposed to hazardous waste sites for similar periods of time. However, at current low levels of exposure in the workplace, it may be difficult to demonstrate effects. There is a large database describing the effects of intermediate-duration inhalation exposures in animals (Adkins et al. 1986; Bi et al. 1985; Drew et al. 1983; Du et al. 1979; Feron et al. 1979a, 1979b; Hong et al. 1981; Lee et al. 1978; Lester et al. 1963; Maltoni et al. 1981; Mirkova et al. 1978; Sal’nikova and Kotsovskaya 1980; Schaffner 1978; Sharma and Gehring 1979; Short et al. 1977; Sokal et al. 1980; Suzuki 1978, 1981; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980). Animals exposed to vinyl chloride vapor for more than 2 weeks and less than a year have experienced effects on the liver, kidneys, lungs, and blood (Bi et al. 1985; Du et al. 1979; Feron et al. 1979a, 1979b; Lester et al. 1963; Sal’nikova and Kotsovskaya 1980; Schaffner 1978; Sokal et al. 1980; Torkelson et al. 1961;

Wisniewska-Knypl et al. 1980). Data were sufficient to determine an intermediate-duration inhalation MRL based on liver effects. However, the MPL was based on a LOAEL and a no-effect level in animals would be more suitable for MRL derivation. Extremely limited information was available regarding oral intermediate-duration effects. One chronic study presented interim sacrifice data that identified relative weight and histopathological changes in the liver (Feron et al. 1981). However, only a single-dose group was compared to controls, precluding determination of the dose-response of the effects observed. Thus, no MRL for oral intermediate-duration exposures could be determined. Additional studies examining the effects of oral exposure to vinyl chloride would be helpful for predicting effects that might be observed in humans consuming contaminated drinking water or foods over a similar period of time. As noted above, absorption of vinyl chloride vapor through the skin is not expected to be significant (Hefner et al. 1975a); thus, additional dermal exposure studies do not seem warranted. However, if further toxicokinetics studies contradict these findings, other intermediate-duration dermal exposure studies may be needed.

Chronic-Duration Exposure and Cancer. A large number of studies of workers exposed to vinyl chloride have identified a wide range of target organs that may be affected by chronic-duration inhalation of vinyl chloride (Bao et al. 1988; Bencko et al. 1988; Berk et al. 1975; Black et al. 1983, 1986; Bogdanikowa and Zawilska 1984; Brugnami et al 1988; Byren et al. 1976; Creech and Johnson 1974; Dinman et al. 1971; Falk et al. 1974; Freudiger et al. 1988; Fucic et al. 1995; Gedigke et al. 1975; Grainger et al. 1980; Harris and Adams 1967; Jayson et al. 1976; Jones and Smith 1982; Langauer-Lewowicka et al. 1976; Laplanche et al. 1987; Lee et al. 1977b; Lilis et al. 1975; Liss et al. 1985; Lloyd et al. 1984; Magnavita et al. 1986; Maricq et al. 1976; Markowitz et al. 1972; Marsteller et al. 1975; Micu et al. 1985; Miller 1975; NOSH 1977; Perticoni et al. 1986; Popper and Thomas 1975; Popper et al. 1981; Preston et al. 1976; Sakabe 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Tamburro et al. 1984; Veltman et al. 1975; Vihko et al. 1984; Walker 1976; Ward 1976; Wilson et al. 1967; Wong et al. 1991). The target organs include the liver, lungs, blood, immune system, cardiovascular system, skin, bones, nervous system, and the reproductive organs. These studies are severely limited in that individual exposure levels have not been documented. In general, studies in animals provide supportive evidence for these effects and give indications of the exposure levels that may be associated with them (Bi et al. 1985; Feron and Kroes 1979; Feron et al. 1979a, 1979b; Lee et al. 1981; Viola 1970; Viola et al. 1971).

No information was available regarding chronic-duration oral exposure in humans. However, studies in animals indicate that the liver, blood, and skin are target organs for oral exposure to vinyl chloride (Feron et al. 1981; Knight and Gibbons 1987; Til et al. 1983, 1991). A chronic-duration oral MRL of 0.00002 mg/kg/day was derived from a LOAEL based on liver effects in rats (Til et al. 1983, 1991).

No information was available regarding effects of chronic-duration dermal exposure in humans or animals, but absorption of vinyl chloride through the skin was not significant in an acute-duration exposure study in monkeys (Hefner et al. 1975a). Thus, dermal exposure studies do not seem warranted. However, if further toxicokinetics studies contradict these findings, then other intermediate-duration dermal exposure studies may be needed.

There is sufficient evidence to indicate that vinyl chloride is carcinogenic to humans (Belli et al. 1987; Brugnami et al. 1988; Byren et al. 1976; Chung and Keh 1987; Cooper 1981; Creech and Johnson 1974; Davies et al. 1990; Fitzgerald and Griffiths 1987; Fox and Collier 1977; Gelin et al. 1989; Geryk and Zudova 1986; Hagmar et al. 1990; Heldass et al. 1987; Infante et al. 1976b; Jones et al. 1988; Monson al. 1975; Pirastu et al. 1990; Rinsky et al. 1988; Smulevich et al. 1988; Teta et al. 1990; Waxweiler et al. 1981; Weber et al. 1981; Williamson and Ramsden 1988; Wong et al. 1991; Wu et al. 1989) and animals (Bi et al. 1985; Drew et al. 1983; Feron and Kroes 1979; Feron et al. 1979a; Froment et al. 1994; Lee et al. 1978; Maltoni et al. 1981; Viola et al. 1971) exposed via inhalation, and in animals exposed via the oral route (Feron et al. 1979a; Maltoni et al. 1981; Til et al. 1983, 1991). The mechanism for carcinogenicity appears to be associated with the formation of reactive intermediates.

Genotoxicity. There are substantial data on clastogenesis in humans exposed to vinyl chloride that indicate that this chemical acts as a potent genotoxicant (Anderson et al. 1980; Ducatman et al. 1975; Fucic et al. 1990, 1995; Funes-Cravioto et al. 1975; Hansteen et al. 1978; Hrivnak et al. 1990; Kucerova et al. 1979; Marion et al. 1991; Purchase et al. 1978). These findings are supported by both animal studies and *in vitro* studies that show positive genotoxicity in a variety of microbial organisms, cultured cell lines, and isolated nucleic acid assays (Anderson and Richardson 1981; Andrews et al. 1976; Bartsch 1976; Bartsch et al. 1976; Bolt et al. 1986; Ciroussel et al. 1990; de Meester et al. 1980; Eberle et al. 1989; Froment et al. 1994; Green and Hathway 1978; Gwinner et al. 1983; Hansteen et al. 1978; Huberman et al. 1975; Jacobsen et al. 1989; Kandala et al. 1990; Laib and Bolt 1977; Laib et al. 1989; Loprieno et al. 1977; McCann et al. 1975; Osterman-Golkar et al. 1977;

Poncelet et al. 1980; Rannug et al. 1974, 1976; Simmon et al. 1977; Singer et al. 1987; Victorin and Stahlberg 1988a; Walles et al. 1988). There are also data supporting the premise that it is the chloroethylene oxide metabolite that is ultimately responsible for the direct action on the DNA (Jacobsen et al. 1989; McCann et al. 1975; Rannug et al. 1974, 1976), and that the mechanism involves alkylation and subsequent base-pair substitution (Bar-bin et al. 1985a). Recent data suggest that chloroacetaldehyde might also be responsible for the mutagenic effects of vinyl chloride (Matsuda et al. 1995). There is a study that indicates that the clastogenic effects of vinyl chloride exposure in humans are reversible (Anderson et al. 1980). Additional studies on the fate of the alkylated DNA in workers after an exposure-free interval would be useful for predicting the mechanisms involved in the latency period for carcinogenesis. In addition, further work elucidating the genotoxic role of chloroacetaldehyde would be useful in explaining the inconsistent findings regarding the effects of this metabolite on clastogenesis and the induction of carcinogenesis.

Reproductive Toxicity. Data from a number of epidemiological studies provide suggestive evidence of adverse effects on male and female reproductive function. Sexual impotence and decreased androgen levels were found in men exposed occupationally to vinyl chloride (Suciu et al. 1975; Veltman et al. 1975; Walker 1976). In women exposed to vinyl chloride, menstrual disturbances and an increased incidence of elevated blood pressure and edema during pregnancy (preeclampsia) were observed (Bao et al. 1988). Although no reports of two-generation reproduction studies in animals were located, two studies examining a range of toxic effects in rats indicate that vinyl chloride is toxic to the testes (Bi et al. 1985; Sokal et al. 1980). A two-generation reproduction study in animals would be helpful to assess whether adverse effects on the rate of conception could be correlated with damage to the male reproductive organs or whether disturbances in female menstrual activity could be verified. Animal models of preeclampsia could be tested to determine the mechanism by which vinyl chloride might cause this effect. Well-designed and well-conducted epidemiological studies examining such changes would also be helpful. No data are available on the possible reproductive toxicity resulting from oral exposure to vinyl chloride. Oral studies that use drinking water as the vehicle of administration would be particularly useful because contaminated groundwater is a potentially significant source of human exposure. The PBPK model would be useful for assessing reproductive toxicity resulting from oral exposure to vinyl chloride.

Developmental Toxicity. The epidemiological studies that have addressed developmental toxicity in offspring of humans who have been exposed to vinyl chloride are controversial. Although some of these purport to show a significant association between birth defects and vinyl chloride exposure (Infante 1976; Infante et al. 1976a, 1976b; NIOSH 1977), their design and analysis have been severely criticized (Hatch et al. 1981; Stallones 1987). At this time, there are insufficient human data to provide a definitive answer to this question. A well-designed and well-conducted epidemiological study examining potential developmental end points would be helpful. There are data showing that vinyl chloride is a developmental toxicant in animals when exposure is by inhalation (John et al. 1977, 1981; Mirkova et al. 1978; Sal'nikova and Kotsovskaya 1980; Ungvary et al. 1978). Continuous lowlevel exposure appears to be the most toxic (Mirkova et al. 1978; Ungvary et al. 1978), but the studies that indicate this are flawed. Additional studies examining exposure to low levels of vinyl chloride throughout gestation would be helpful in settling this issue. This issue is particularly important because women living in the vicinity of hazardous waste sites have the potential to be exposed to low levels of vinyl chloride on a continuous basis. It would also be helpful to determine whether pregnancy increases the susceptibility to vinyl chloride in the mother. Also, studies in animals suggest that offspring exposed in *utero* may experience adverse effects after birth (Mirkova et al. 1978; Sal'nikova and Kotsovskaya 1980), although these studies are also flawed. It is anticipated that a combined two-generation reproductive and developmental inhalation study will be conducted by the Chemical Manufacturers Association under a Memorandum of Understanding with ATSDR. There are no data for oral exposures. Because of this deficiency, oral studies examining a range of developmental end points would be useful in assessing the possibility of these effects in humans. The PBPK model would be a useful tool in such risk assessment.

Immunotoxicity. Studies of workers occupationally exposed to vinyl chloride suggest that the immune system may be activated by vinyl chloride (Bogdanikowa and Zawilska 1984). Some data suggest that reactive intermediates may bind to proteins in the body, sufficiently altering them so that they become antigenic (Grainger et al. 1980). In some instances, an autoimmune-like syndrome develops. The likelihood of this may be associated with the possession by individuals of specific genetic determinants (HLA alleles) (Black et al. 1983, 1986). Because of the low incidence of the autoimmune response in humans, the immunotoxicity may be best further studied in one of the strains of mice known to have a propensity for developing autoimmune diseases. Also, additional epidemiological studies examining the immune response of exposed populations may be helpful.

Neurotoxicity. A number of studies in humans (Lester et al. 1963; Patty et al. 1930) and animals (Hehir et al. 1981; Jaeger et al. 1974; Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930) demonstrate that vinyl chloride is a central nervous system depressant following brief high-level inhalation exposures. Two studies in animals have also found degenerative effects in central nervous system tissue following chronic inhalation exposure to high levels of vinyl chloride (Viola 1970; Viola et al. 1971). It is unknown whether these degenerative changes might also occur at lower doses; thus, a study examining the effects of a range of lower doses would be informative. In addition, relatively recent studies present suggestive evidence that vinyl chloride may also produce peripheral nerve damage in humans exposed chronically via inhalation (Langauer-Lewowicka et al. 1976; Magnavita et al. 1986; Perticoni et al. 1986; Sakabe 1975; Walker 1976). Animal studies examining histopathological and electrophysiological end points in peripheral nerves would be helpful for assessing what doses may be associated with this effect. Epidemiological studies examining exposed populations for subclinical peripheral nerve damage would be helpful. Oral exposure studies in animals would be beneficial for assessing the likelihood that populations exposed to contaminated water might develop symptoms of neurotoxicity.

Epidemiological and Human Dosimetry Studies. Virtually all of the data on effects in humans following inhalation exposure to vinyl chloride come from epidemiological studies of workers exposed during the production of PVC (Bao et al. 1988; Bencko et al. 1988; Berk et al. 1975; Black et al. 1983, 1986; Bogdanikowa and Zawilska 1984; Brugnami et al. 1988; Byren et al. 1976; Creech and Johnson 1974; Dinman et al. 1971; Falk et al. 1974; Freudiger et al. 1988; Gedigke et al. 1975; Grainger et al. 1980; Harris and Adams 1967; Jayson et al. 1976; Jones and Smith 1982; Langauer-Lewowicka et al. 1976; Laplanche et al. 1987; Lee et al. 1977b; Lilis et al. 1975; Liss et al. 1985; Lloyd et al. 1984; Magnavita et al. 1986; Maricq et al. 1976; Markowitz et al. 1972; NIOSH 1977; Popper et al. 1981; Preston et al. 1976; Sakabe 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Tamburro et al. 1984; Veltman et al. 1975; Vihko et al. 1984; Walker 1976; Ward 1976; Wilson et al. 1967; Wong et al. 1991). These studies are limited by the absence of information on individual exposure levels. Also, in North America and Western Europe, only limited numbers of females have been studied.

For the most part, studies examining the carcinogenic potential of vinyl chloride have been adeqluate to distinguish an increased incidence of the rare cancer, angiosarcoma (Byren et al. 1976; Creech and Johnson 1974; Fox and Collier 1977; Infante et al. 1976b; Jones et al. 1988; Monson al. 1975; Pirasm

et al. 1990; Rinsky et al. 1988; Teta et al. 1990; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989). However, many studies have used cohorts that are too small to detect smaller increases in other types of cancer (respiratory, central nervous system, lymphatic, or hematopoietic). Epidemiological studies designed to investigate reproductive and developmental effects of vinyl chloride have not been useful, in part because of a poor choice of statistical analysis, inadequate controls, lack of effects due to current low levels of exposure, or failure to take into account other chemical exposures. Additional cohort studies of these end points would be useful for examining these effects in humans.

Clastogenic effects have been used as a dosimeter for exposures to radioactive substances, and work has been done to use this approach for chemical exposures as well. More data on quantified exposures and well-controlled cytogenetic studies would be useful in developing a method for monitoring populations living near hazardous waste sites.

In addition, as noted above, well-designed and well-conducted epidemiological studies examining the incidence of peripheral neuropathies, developmental toxicity (birth defects, miscarriages, delayed prenatal development, postnatal hepatotoxicity), reproductive toxicity (male infertility, menstrual irregularity, preeclampsia in pregnant women), and immune reactivity in exposed populations would also be helpful.

Biomarkers of Exposure and Effect

Exposure. Several potential biomarkers for exposure to vinyl chloride have been identified. Vinyl chloride measured in expired air is an adequate indicator of recent, moderate-to-high-level exposure (Baretta et al. 1969). However, for low-level exposures or exposures that occur over l-2 hours prior to the time of measurement, this biomarker is not useful. Thiodiglycolic acid, a major urinary metabolite of vinyl chloride, has been used to monitor workers occupationally exposed to vinyl chloride (Muller et al. 1979). However, this biomarker is rapidly excreted, and therefore, the period of its utility is limited (Watanabe and Gehring 1976; Watanabe et al. 1979b). Also, thiodiglycolic acid is not specific for vinyl chloride; it may also be produced as a result of the metabolism of l,l-dichloroethene, ethylene oxide, or 2,2-dichloroethylether (Norpoth et al. 1986; Pettit 1986).

The DNA adducts l,N6-ethenoadenosine and 3,p-ethenocytidine may be used to indicate vinyl chloride exposure, although studies correlating the levels of these adducts with exposure levels are still lacking. These products remain in the body longer than free vinyl chloride or thiodiglycolic acid, thereby increasing the period after exposure that a potential exposure may be detected (Bolt 1986; Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1987a, 1987b). However, the presence of these adducts cannot indicate how long it has been since exposure occurred. In addition, these adducts are formed as the result of binding of the intermediary metabolites with nucleic acids, and other compounds producing the same intermediary metabolites will also produce these adducts. For example, these adducts have been identified as a result of exposure to vinyl bromide, ethyl carbamate, acrylonitrile, 2-cyanoethylene, and 1,2-dichloroethane (Bolt et al. 1986; Svensson and Osterman-Golkar 1986). Studies attempting to identify a metabolite more specific to vinyl chloride may be helpful in developing a biomarker that may be used to facilitate future medical surveillance, which can lead to early detection and possible treatment.

Effect. With regard to biomarkers of effect of vinyl chloride exposure, numerous indicators have been examined. The central nervous system depression associated with brief high-level exposures is easily determined by observation. The hepatic changes that may develop during longer term exposures are difficult to detect by standard biochemical liver function tests (Berk et al. 1975; Du et al. 1995; Liss et al. 1985; Vihko et al. 1984). In contrast, tests of clearance such as the indocyanine clearance test or measurement of serum bile acid levels are more specific and sensitive indicators of vinyl chloride-induced liver damage (Berk et al. 1975; Liss et al. 1985; Vihko et al. 1984). Angiosarcoma of the liver is a rare tumor type that has been shown to result from vinyl chloride exposure. However, other agents are known to cause angiosarcoma of the liver, such as arsenic and Thorotrast@ (Gedigke et al. 1975; Marsteller et al. 1975). Enzyme-linked immunoassay (EIA) has been used to detect anti-p53 antibodies in the serum of some individuals with angiosarcoma of the liver before clinical diagnosis of this lesion was made (Trivers et al. 1995). However, not all individuals who develop angiosarcoma of the liver test positive for anti-p53 antibodies; in addition, anti-p53 bodies are not specific only to angiosarcoma of the liver. Further investigation into the ability of this assay to predict individuals at increased risk for developing angiosarcoma of the liver would be useful. Measurement of chromosomal aberrations may indicate the genotoxic effects of vinyl chloride (Anderson et al. 1980; Ducatman et al. 1975; Fucic et al. 1990). However, these aberrations do not specifically indicate vinyl chloride-induced damage. Also, DNA adducts may signal the potential to develop genotoxic effects. Further work identifying the correlation between the adducts and genotoxic effects would be useful.

The cyanosis and blanching of the fingers in response to exposure to the cold may be an early indicator for the development of vinyl chloride disease. However, other conditions also known to cause these symptoms include connective tissue disorders, mechanical arterial obstruction, hyperviscosity of the blood, and exposure to drugs, chemicals, or vibrating tools (Black et al. 1983, 1986; Freudiger et al. 1988). The presence of basophilic stippled erythrocytes has been reported after inhalation exposure of mice to vinyl chloride (Kudo et al. 1990). Further study is needed to determine whether this parameter could be used as a biomarker of effect in humans.

Absorption, Distribution, Metabolism, and Excretion. There are few data on humans for all toxicokinetic parameters across all exposure routes (Krajewski et al. 1980; Sabadie et al. 1980). There are a number of animal studies describing the absorption, distribution, metabolism, and excretion of vinyl chloride administered via the oral route (Feron et al. 1981; Green and Hathway 1978; Watanabe and Gehring 1976; Watanabe et al. 1987a, 1987b; Withey 1976) and the inhalation route (Bolt et al. 1976a, 1977; Buchter et al. 1977, 1980; Filser and Bolt 1979; Guengerich and Watanabe 1979; Hefner et al. 1975b; Jedrychowski et al. 1984, 1985; Ungvary et al. 1978; Watanabe and Gehring 1976; Watanabe et al. 1978a, 1978b; Withey 1976) but few describing the toxicokinetics of vinyl chloride administered via the dermal route. One study in monkeys found an extremely limited absorption of vinyl chloride vapor across the skin (Hefner et al. 1975a). However, only two animals were used, and this was the only study located that examined toxicokinetics after dermal exposure. If there is negligible absorption resulting from dermal exposure, then additional studies examining toxicokinetics from dermal exposures are not warranted; another study verifying the limited nature of dermal absorption, however, would be reassuring. Furthermore, the intermediary metabolites of vinyl chloride appear to be responsible for many of the toxic effects observed. Therefore, information regarding differences in the metabolic pattern according to sex, age, nutritional status, and species and correlations to differences in health effects would also be useful.

Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion of vinyl chloride have been studied in animals (Bolt et al. 1976a, 1977; Buchter et al. 1977, 1980; Feron et al. 1981; Filser and Bolt 1979; Green and Hathway 1975; Guengerich and Watanabe 1979; Hefner et al. 1975b; Jedrychowski et al. 1984, 1985; Ungvary et al. 1978; Watanabe and Gehring 1976; Watanabe et al. 1976a, 1976b, 1978a, 1978b; Withey 1976), but information on toxicokinetics in humans is extremely limited (Krajewski et al. 1980; Sabadie et al. 1980). Human and animal data indicate that similar target organs (liver, central nervous system) for the toxic effects of vinyl chloride exist,

suggesting some similarities of kinetics. Limited information is available regarding interspecies differences in kinetics. Most toxicokinetic studies have been conducted using rats (Bolt et al. 1976a, 1977; Buchter et al. 1977; Feron et al. 1981; Filser and Bolt 1979; Green and Hathway 1975; Guengerich and Watanabe 1979; Hefner et al. 1975b; Jedrychowski et al. 1984, 1985; Ungvary et al. 1978; Watanabe and Gehring 1976; Watanabe et al. 1976a, 1976b, 1978a, 1978b; Withey 1976), but one study in primates indicates that metabolism may saturate at lower concentrations in primates than rats (Buchter et al. 1980). This may suggest a lower saturation point in humans also. Modeling studies might continue to provide information on the toxicokinetics of vinyl chloride in humans.

Methods for Reducing Toxic Effects. Vinyl chloride appears to be rapidly and completely absorbed following inhalation and oral exposure (Bolt et al. 1977; Krajewski et al. 1980; Watanabe et al. 1976a; Withey 1976). Methods used to reduce absorption immediately after exposure include removal from the source of exposure, cleansing contaminated body parts, and in cases of ingestion, speeding the removal of unabsorbed material from the gastrointestinal tract (Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Ulin 1992). No information was located regarding the mechanism of absorption. Additional experiments examining the mechanism of absorption and potential means of interfering with that mechanism would be useful. Distribution of vinyl chloride in the body is rapid and widespread, but storage is limited by rapid metabolism and excretion (Bolt et al. 1976a; Buchter et al. 1977; Watanabe et al. 1976a, 1976b, 1978a). The toxicity of vinyl chloride has been attributed to the formation of reactive epoxide metabolites. No information was located regarding removal of these toxic metabolites from the body once they have been formed, but information from toxicokinetic studies suggest that vinyl chloride metabolism to toxic metabolites may be reduced. Saturation of the metabolic pathways for vinyl chloride can result in the clearance of unmetabolized vinyl chloride in exhaled air (Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a, 1976b, 1978a). Studies examining the effectiveness and endogenous toxicity of the agents used to block the metabolic pathways (cobaltous chloride, SKF-535-A, 6-nitro-1,2,3-benzothiadiazole) would provide useful information. Another strategy for reducing the formation of toxic metabolites includes increasing the pool of glutathione for use in metabolism to nontoxic metabolites. Studies examining the effectiveness of this procedure would also be helpful. Vinyl chloride disease may be mediated by an autoimmune mechanism (Grainger et al. 1980; Ward 1976). Further studies continuing to examine the role of autoimmune responses in vinyl chloride disease, the genetic factors resulting in greater susceptibility to the disease, and the effectiveness of drugs that

block immune responses in reducing the symptoms of vinyl chloride disease would also provide valuable information.

2.10.3 On-going Studies

On-going studies regarding the health effects of vinyl chloride were reported in the Federal Research in Progress File (FEDRIP 1994) database and the CRISAJSDA (1994) database. Table 2-8 presents a summary of on-going studies that address the health effects of vinyl chloride. It is anticipated that a combined two-generation reproductive and developmental inhalation study will be conducted by the Chemical Manufacturers Association under a Memorandum of Understanding with ATSDR.

TABLE 2-8. On-going Studies on Vinyl Chloride[a]

Investigator	Affiliation	Research description	Sponsor
I. Hertz-Piccioto	University of North Carolina at Chapel Hill	Measuring biomarkers of genotoxicity and human variability in response to vinyl chloride	NIEHS
J. Miller	University of Wisconsin at Madison	Metabolism and DNA adducts of vinyl chloride and its epoxide in rodent and human tissues	NCI
R. Prough	University of Louisville Medical School	Biochemical biomarkers of exposure; metabolism of vinyl chloride in rat and human hepatocytes	NIEHS
S. Rappaport	University of North Carolina at Chapel Hill	Dose-response relationships for adducts of hemoglobin and serum albumin for use as biomarkers of exposure	NIEHS
B. Singer	University of California, Lawrence Berkeley Laboratory	Biochemical mechanisms of vinyl chloride carcinogenesis	NCI
T. Skopek	University of North Carolina at Chapel Hill	Frequency and distribution of mutations induced by vinyl chloride at (hprt) locus in mouse model and human lymphoblastoid cells *in vitro*	NIEHS
J. Solomon	New York University Medical Center	Formation of 3-alkyl uracil adducts from aliphatic epoxides in rats after inhalation exposure	NIEHS
J. Swenberg	University of North Carolina at Chapel Hill	Comparison of formation of DNA adducts in target and nontarget tissues and in peripheral blood lymphocytes	NIEHS
J. Wong	University of Louisville, Belknap Campus	Produce monoclonal antibodies to synthetic antigens of vinyl chloride metabolites	NIEHS

[a]Sources: CRIS/USDA (1994); FEDRIP (1994)

DNA = deoxyribonucleic acid; NCI = National Cancer Institute; NIEHS = National Institute of Environmental Health Sciences